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Review

Subtribe Hyptidinae (Lamiaceae): A promising source of bioactive metabolites

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ABSTRACT

Ethnopharmacological relevance: The subtribe Hyptidinae contains approximately 400 accepted species distributed in 19 genera (*Hyptis*, *Eriope*, *Condea*, *Cantinoa*, *Mesosphaerum*, *Cyanocephalus*, *Hypenia*, *Hyptidendron*, *Oocephalus*, *Medusantha*, *Gymneia*, *Marsypianthes*, *Leptohyptis*, *Martianthus*, *Asterohyptis*, *Eplingiella*, *Physominthe*, *Eriopidion* and *Rhaphiodon*). This is the Lamiaceae clade with the largest number of species in Brazil and high rates of endemism. Some species have been used in different parts of the world mainly as insecticides/pest repellents, wound healing and pain-relief agents, as well as for the treatment of respiratory and gastrointestinal disorders.
Aim of the review: This review aims to discuss the current status concerning the taxonomy, ethnobotanical uses, phytochemistry and biological properties of species which compose the subtribe Hyptidinae.
Materials and methods: The available information was collected from scientific databases (ScienceDirect, Pubmed, Web of Science, Scopus, Google Scholar, ChemSpider, SciFinder ACS Publications, Wiley Online Library), as well as other literature sources (e.g. books, theses).
Results: The phytochemical investigations of plants of this subtribe have led to the identification of almost 300 chemical constituents of different classes such as diterpenes, triterpenes, lignans, α-pyrones, flavonoids, phenolic acids and monoterpenes and sesquiterpenes, as components of essential oils. Extracts, essential oils and isolated compounds showed a series of biological activities such as insecticide/repellent, antimicrobial and anti-nociceptive, justifying some of the popular uses of the plants. In addition, a very relevant fact is that several species produce podophyllotoxin and related lignans.
Conclusion: Several species of Hyptidinae are used in folk medicine for treating many diseases but only a small fraction of the species has been explored and most of the traditional uses have not been validated by current investigations. In addition, the species of the subtribe appear to be very promising as alternative sources of podophyllotoxin-like lignans which are the lead compounds for the semi-synthesis of teniposide and etoposide, important antineoplastic agents. Thus, there is a wide-open door for future studies, both to support the popular uses of the plants and to find new biologically active compounds in this large number of species not yet explored.

1. Introduction

The Hyptidinae, a subtribe of the Lamiaceae family, currently contains 19 genera and around 400 species which are herbs and shrubs distributed mainly in tropical America, from the southern United States and the Caribbean, to Argentina. Some species were introduced in the Old World as weeds and two species occur naturally in tropical Africa. Brazil has the main diversity within the subtribe, with occurrence of species in different vegetations, especially the Atlantic Rain Forest and Cerrado, region that includes the states of Minas Gerais, Bahia, Goiás, among others (Harley et al., 2004, 2012; Pastore et al., 2011; Harley and Pastore, 2012).

Abbreviations: list: MIC, minimal inhibitory concentration; ATCC, American Type Culture Collection; HIV, human immunodeficiency virus; CNS, central nervous system; KB cells, subline of the ubiquitous keratin-forming tumor cell line HeLa; MCF-7, breast cancer cell line; HCT-8, human ileocecal adenocarcinoma cell line; B-16, melanoma cell line; ED_{50}, effective dose for 50% of the population; DPPH, 2,2-diphenyl-1-picrylhydrazyl radical; CLP, cecal ligation and puncture; CYP, cytochrome P-450; IC_{50}, half maximal inhibitory concentration; SC_{50},, the concentration that causes a decrease in the initial DPPH concentration by 50%; LC_{50},, the concentration of the compound in that is lethal for 50% of exposed population.

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Several plants of this taxon are covered with glandular trichomes that produce and store essential oils. Due to the odor conferred by these oils, the plants are very popular in rural areas of Latin America, where they are used as pest repellents and for treating respiratory and gastrointestinal disorders, among others (Agra et al., 2007; Pinheiro et al., 2015; Arruda et al., 2016). Activities such as antinociceptive, antimicrobial and insecticidal have been reported, endorsing the traditional use of some species (Nascimento et al., 2008; McNeil et al., 2011).

Besides the research papers published over the years, some reviews concerning species of Hyptidinae have appeared in the scientific literature (Piozzi et al., 2009; McNeil et al., 2011; Picking et al., 2013). A review on *Hyptis,* the largest genus of the subtribe, was recently published (Sedano-Partida et al., 2020a), pointing out the importance of these plants.

Phytochemical assessments carried out with species of Hyptidinae have revealed the presence of monoterpenes and sesquiterpenes, composing the essential oils, diterpenes, triterpenes, flavonoids, lignans, phenolic acids and α-pyrones. Some of the biological effects exhibited by these species are attributed to the presence of the above-mentioned classes of specialized metabolites.

This paper makes a comprehensive review of the botanical aspects, traditional uses, phytochemistry and biological activities of Hyptidinae species published until May 2020 aiming at highlighting the relevance of further research with this almost exclusively neotropical group of plants, so far partially explored.

2. Notes on the taxonomy of Hyptidinae

Lamiaceae has about 250 genera and 7200 species, occurring in tropical to temperate areas worldwide, except Antarctica. In Brazil, there are approximately 500 native species, with some genera and species introduced and naturalized (Harley, 1988, 2012; Harley et al., 2004; Harley and Pastore, 2012).

The family is subdivided into nine subfamilies, six of them occurring in South America (Viticoideae, Ajugoideae, Scutellarioideae, Lamioideae, Callicarpoideae and Nepetoideae) (Li and Olmstead, 2017). The species of the subfamily Nepetoideae, which occur in tropical America, are distributed into two tribes: Mentheae, a mainly temperate group, and Ocimeae, a tropical group in which is included the subtribe Hyptidinae. Hyptidinae encompasses approximately 400 species mainly occurring in the Neotropical region. These species were formerly distributed into nine genera of which the largest was the genus *Hyptis* with more than 300 species (Harley, 1988).

A phylogenetic analysis carried out by Pastore et al. (2011), using molecular data, pointed out the need for modifications in the classification of the taxon. Based on this study, 12 new genera were recognized, augmenting the subtribe to 19 genera (Harley and Pastore, 2012). Consequently, Hyptidinae comprises the genus *Hyptis* with approximately 144 species, the genera *Eriope*, *Condea*, *Cantinoa*, *Mesosphaerum*, *Cyanocephalus* and *Hypenia*, with 20–30 species and the genera *Hyptidendron* and *Oocephalus*, including about 20 species, each one. The other genera have less than 10 species: *Medusantha* (eight species), *Gymneia* (six species), *Marsypianthes* (five species), *Leptohyptis* (five species), *Martianthus* (four species), *Asterohyptis* and *Eplingiella* (3–4 species) and *Physominthe*, with two species. Finally, the subtribe includes the monotypic genera *Eriopidion* and *Rhaphiodon* (Harley and Pastore, 2012). This is the Lamiaceae clade with the largest number of species in Brazil (Harley, 2012; Harley and Pastore, 2012), presenting high rates of endemism (Harley, 2014).

After the rearrangement of the subtribe, the names of many species were altered. Therefore, in this review the species are presented by the accepted nomenclature and, in parenthesis, it is shown the names that appear in the publications.

3. Ethnobotanical uses

Altogether, approximately 20 species of Hyptidinae were the focus of ethnobotanical studies, not just as medicinal plants but also as insecticidal or repellent agents. In fact, an article dating from 1950 reported that the whole plant *Cantinoa americana* (Aubl.) Harley & J.F.B.Pastore (syn. *Hyptis spicigera* Lam.), strongly aromatic, was used to ward off termites and mosquitoes (Grindley, 1950). Some species have morphological similarities and are known by the same popular names (Bordignon, 1990). Therefore, they may be used interchangeably by the population. The detailed traditional uses are given in Table 1.

Among the species cited in ethnobotanical studies, *Mesosphaerum suaveolens* (L.) Kuntze (syn. *Hyptis suaveolens* (L.) Poit.) appears in the first place with several medical indications such as anti-inflammatory and in the treatment of gastrointestinal ailments (Bieski et al., 2015, 2012; de Jesus et al., 2009; de Sousa Araújo et al., 2008). *Hyptis crenata* Pohl ex Benth and *Mesosphaerum pectinatum* (L.) Kuntze (syn. *Hyptis pectinata* (L.) Poit.) are also widely cited in ethnobotanical reports (Elisabetsky and Posey, 1989; Amorozo, 2002; Teixeira and De Melo, 2006; Albuquerque and Oliveira, 2007; Oliveira et al., 2011; Cavalcanti and Albuquerque, 2013; Yazbek et al., 2016; Griz et al., 2017). Most of these studies report the uses of species that occur in Cerrado and in a region geographically adjacent called "Caatinga", an exclusively Brazilian semi-arid biome located almost entirely within Northeast Brazil. It is worth mentioning that most of the cited species do not have their uses scientifically proven by experimental studies.

4. Phytochemistry

Plants from Hyptidinae produce several classes of specialized metabolites. The compounds isolated until now belong to the classes of diterpenes (**1**–**73**), triterpenes (**74**–**113**), lignans (**114**–**148**), α-pyrones (**149**–**191**), flavonoids (**192**–**221**), phenolic acids (**222**–**236**) and monoterpenes and sesquiterpenes, as components of essential oils (**237**–**295**). Alkaloids are very rare in this group of plants. Although there are reports of detection of alkaloids using phytochemical and histochemical screenings, the only compound identified was (*R*)-5-hydroxypyrrolidin-2-one, isolated from *Condea verticillata* (Jacq.) Harley & J.F.B.Pastore (syn. *Hyptis verticillata* Jacq.) (Kuhnt et al., 1995).

4.1. Diterpenes

Most diterpenes found in Hyptidinae are of the abietane type, although some labdane, isopimarane and kaurane have also been reported. Their structures are shown in Fig. 1. The first studies were published in the years 1970, and reported the isolation of horminone (**1**), 14-methoxytaxodione (**2**) and hyptol (**3**) from *Eplingiella fruticosa* (Salzm. ex Benth.) Harley & J.F.B.Pastore (syn. *Hyptis fruticosa* Salzm. ex Benth) (Marletti et al., 1976). Suaveolic acid (**4**) and suaveolol (**5**) were obtained from the leaves of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) (Manchand et al., 1974; Prawatsri et al., 2013). The last mentioned species also afforded 13α-*epi*-dioxiabiet-8(14)-en-18-ol (**6**) (Chukwujekwu et al., 2005), isosuaveolic acid (**7**), 8α,9α-epoxysuaveolic acid (**8**) and 14-*O*-methylsuaveolic acid (**9**) (Prawatsri et al., 2013). In 1990, umbrosone (**10**) was obtained from *Mesosphaerum sidifolium* (L.Hérit) Harley & J.F.B.Pastore (syn. *Hyptis umbrosa* Salzm. ex Benth.) (Delle Monache et al., 1990).

Studies carried out with the aerial parts of *Hyptis dilatata* Benth. led to the isolation of epimethylrosmanol (**11**), epiethylrosmanol (**12**), rosmanol (**13**), carnosol (**14**), methylrosmanol (**15**), ethylrosmanol (**16**), isorosmanol (**17**), epirosmanol (**18**), carnosic acid (**19**), carnosic acid methyl ester (**20**), pisiferic acid methyl ester (**21**) and esquirolin B (**22**) (Urones et al., 1998).

The roots of *Hyptis comaroides* Harley & J.F.B.Pastore (syn. *Peltodon longipes* A.St.-Hill ex Bentham) seem to be a source of abietane diterpenes. The species afforded the compounds horminone (**1**), inuroyleanol

Table 1
Ethnobotanical studies reported for Hyptidinae species.

Species	Country regions	Part of the plant	Preparation	Ethnobotanical uses	References
***Mesosphaerum suaveolens* (syn. *H. suaveolens*)**	Bangladesh	Seeds	n.d.	Gonorrhea, fever, headache	Hossan et al. (2018)
	Bangladesh	Seeds	n.d.	Constipation, weakness	Kadir et al. (2014)
	Bangladesh	Roots	n.d.	Constipation	Rahmatullah et al. (2014)
	Brazil	Leaves and flowers	Infusion; Decoction	Dysmenorrhea, respiratory diseases and as febrifuge	Agra et al., (2007; 2008)
	Brazil	Flowers	Infusion; Decoction	Digestive	Agra et al. (2007)
	Brazil	Flowers	Inhalation cigarette	Toothache and headache	Agra et al. (2007)
	Brazil	Seeds	Put a small seed into the eye	To withdraw small pieces of dust from the eyes.	Agra et al. (2008)
	Brazil	Herb	n.d.	Diaphoretic, several catarrhal diseases, carminative, wound healing	Breitbach et al. (2013)
	Brazil	Leaves	Infusion	Flu, fever, nasal congestion	Lemos et al. (2016)
	Brazil	Leaves, aerial parts, whole plant, roots	Decoction, maceration, infusion	Worms, hemorrhoids, expectorant, intestine, ulcers	Ribeiro et al. (2017)
	Brazil	n.d.	n.d.	Pains in general, rheumatism, renal disorders, inflammation in the ovary	de Santana et al. (2016)
	Brazil	Leaves; flowers	Infusion	Anti-hemorrhagic postpartum	van der Berg (1982); Yazbek et al., (2016)
	Brazil	n.d.	Infusion	Pain, stomach, flu, constipation, kidneys and worms	Bieski et al. (2012)
	Brazil	Leaves	Decoction	Anxiety, nervousness and depression	Bitu et al. (2015)
	Brazil	Flowers, leaves, seeds	n.d.	Digestive problems, menstrual colic, amenorrhea, toothache, headache, fever, influenza, respiratory problems in general, gout, eye cleansing	de Albuquerque et al. (2007)
	China	Aerial parts	Decoction	Cold	Li and Xing (2016)
	India	Leaves	Maceration Topical application	Fever	Chander et al. (2015)
	India	Whole plant	n.d.	Colic, flatulence	Gupta et al. (2018)
	India	Leaves	Maceration Topical application	To cure cuts and wounds	Jeeva and Femila (2012); Sharma et al., (2014)
	India	Whole plant	Maceration	Urinary infection and dysentery	Panda (2014)
	India	Leaves	Maceration Topical application	To treat sores and fungal infections	Policepatel and Manikrao (2013)
	India	Leaves	Juice	Stomachache	Silambarasan and Ayyanar (2015)
	India	Leaves	Decoction	Liver troubles	Choudhury et al. (2015)
	Kenya	Whole plant	n.d.	Mosquitoes repellent	Seyoum et al. (2002)
	Mali	Leaves	Maceration Topical application	Wound healing	Inngjerdingen et al. (2004)
	Malaysia	n.d.	n.d.	Skin infection	Wiart et al. (2004)
	Mexico	n.d.	n.d.	Gastrointestinal disorders	Jacobo-Herrera et al. (2016)
	Nigeria	Leaves	Decoction	To facilitate childbirth reducing the length of labor and labor pains	Attah et al. (2012)
	Nigeria	Leaves	Decoction	Insect repellent against malaria-causing agent	Attah et al. (2012)
	Nigeria	Leaves	Maceration Topical application	Headache	Igoli et al. (2003)
	Nigeria	Leaves	n.d.	Malaria disease	Olorunnisola et al. (2013)
	Nigeria	Leaves	Decoction	Malaria disease	Iyamah and Idu (2015)
	Nigeria	Whole plant	n.d.	Mosquitoes repellent	Sonibare et al. (2015)
	Tanzania	Leaves	Inhalation	Abdominal pains and general body weakness	Chhabra et al. (1990)
	Togo	Leaves	Decoction	Liver diseases	Kpodar et al. (2016)
***Mesosphaerum pectinatum* syn. (*Hyptis pectinata*)**	Brazil	Entire plant	Infusion	Dysmenorrheal and liver disorders	Agra et al. (2007)
	Brazil	Flowers	Infusion	Asthmas, coughs and bronchitis	Agra et al. (2007)
	Brazil	Flowers	Infusion	Against dysmenorrheal and liver disorders.	Agra et al. (2008)
	Brazil	Leaves	Topical application	Wounds	Moreira et al. (2002)
	Brazil	Aerial parts	n.d.	Headache, odontalgia, amenorrhea, hepatalgia, hepatic problems, flatulence, rheumatism, gastritis, ulcer, asthma, cough, bronchitis	de Albuquerque et al. (2007)
	Brazil	n.d.	n.d.	Rhynopharyngitis, nasal congestion, skin diseases, gastric problems, fever, bacterial and fungal infections	Nascimento et al., (2008); de Queiroz et al., (2014)
	Kenya	n.d.	Infusion	Unspecified illnesses	Githinji and Kokwaro (1993)
	Kenya	n.d.	n.d.	Molluscide	Githinji and Kokwaro (1993)
	Mexico	n.d.	n.d.	Gastric disturbances	Jacobo-Herrera et al. (2016)
	Mexico	n.d.	n.d.	Antiseptic	Rojas et al. (1992)
	Tanzania	Whole plant	Decoction	Intestinal worms in children	Chhabra et al. (1990)
***Mesosphaerum sidifolium* (syn. *Hyptis umbrosa*)**	Brazil	Leaves	Juice and decoction	Treatment of nasal and auricular diseases	Agra et al. (2008)
	Brazil	Leaves	Decoction	Stomachic and tonic.	Agra et al. (2008)

(*continued on next page*)

Table 1 (*continued*)

Species	Country regions	Part of the plant	Preparation	Ethnobotanical uses	References
	Brazil	Leaves	Syrup	Expectorant	Agra et al. (2008)
***Cantinoa althaeifolia* (syn. *Hyptis althaeifolia*)**	Brazil	n.d.	n.d.	Flu, stomach, sedative, relaxation	Pirker et al. (2012)
***Cantinoa americana* (syn. *Hyptis spicigera*)**	Bolivia	Fruit	Decoction	Stomachache, stomach disorders, diarrhea	Hajdu and Hohmann (2012)
	Bolivia	Flower	Infusion	Liver disorder	Hajdu and Hohmann (2012)
	Bolivia	Roots	n.d.	Scabies	Hajdu and Hohmann (2012)
	Burkina Faso	Leaves	Maceration	Toothache	Tapsoba and Deschamps (2006)
	Ghana	Leaves	Infusion	Anti-malarial and insect repellent against mosquitoes	Asase et al. (2005)
	Mali	Aerial parts	Decoction Topical application	Wound healing	Inngjerdingen et al. (2004)
	Mali	Leaves	Decoction	Malaria	Diarra et al. (2015)
Hyptis capitata	Bangladesh	Whole plant	Infusion	Abdominal pain	Kadir et al. (2014)
	Bangladesh	Roots	Infusion	Amenorrhea	Kadir et al. (2014)
	Colombia	n.d.	n.d.	Anti-inflammatory and healing of ulcers	Gonzalez (1980)
	Malaysia	Roots	Infusion	Fevers and colds	Ahmad and Holdsworth (2003)
	Peru	Leaves	Inhalation cigarette	Analgesic	Odonne et al. (2013)
	China	Leaves	Topical application	Bruise, rheumatoid arthritis	Zheng et al. (2013)
***Cantinoa mutabilis* (syn. *Hyptis mutabilis*)**	Argentina	Leaves	n.d.	Diaphoretic, carminative and vulnerary	Goleniowski et al. (2006)
	Bolivia	Leaves	Infusion Topical application	Skin ulcer	Hajdu and Hohmann (2012)
	Bolivia	Leaves and roots	Topical application	Leishmaniasis, skin infection, urinary infection, diarrhea, fright[a]	Arévalo-Lopéz et al. (2018)
	Bolivia	Leaves and roots	Decoction	Vomits, diarrhea and fever	Arévalo-Lopéz et al. (2018)
	Brazil	Herb	n.d.	Diaphoretic, several catarrhal disease, carminative, wound healing	Breitbach et al. (2013)
	Brazil	Leaves	Infusion	Menstrual cramps	Yazbek et al. (2016)
	Brazil	Leaves	Decoction; Infusion	Cardiac illness, cold, flu	de Barros et al. (2017)
	Brazil	Leaves	Infusion	Stomach and menstrual cramps	van den Berg and da Silva (1988)
	Mexico	Aerial parts; Leaves	Infusion Topical application	Erysipelas	Andrade-Cetto (2009)
	Peru	Aerial parts	Maceration Topical application	Headache, vertigo in the elderly	Sanz-Biset et al. (2009)
	Suriname	n.d.	n.d.	Headache	van't Klooster et al. (2016)
	Brazil	Bark. Flowers, leaves	n.d.	Uterine inflammation, gastritis, cough, placental delivery, headache, healing, expectorant	de Albuquerque et al. (2007)
***Condea verticilatta* (syn. *Hyptis verticillata*)**	Colombia	n.d.	n.d.	Rheumatism	Gonzalez (1980)
	Mexico	Roots	Infusion	Vomit, asthma, body pain	Alonso-Castro et al. (2012)
	Mexico	n.d.	n.d.	Headache, stomach ache and gastrointestinal disorders	Jacobo-Herrera et al. (2016)
	Nicaragua	Leaves, whole plant, roots	n.d.	Skin conditions of diabetes	Giovannini et al. (2016)
***Condea albida* (syn. *Hyptis albida*)**	Mexico	n.d.	n.d.	Gastrointestinal disturbances, skin infections, rheumatism, cramps, and muscular pains	Martínez (1979)
	Mexico	n.d.	n.d.	Influenza, rheumatic pain, wound healing, antihelmintic	Pereda-Miranda and Delgado (1990); Rojas et al., (1992); Biblioteca Digital de Medicina Tradicional Mexicana (2020)
	n.d.	Leaves	n.d.	Insect repellent	Altschul (1973)
Hyptis brevipes	Brazil	Leaves	Infusion	Stomach and kidneys affections	Oliveira et al. (2011)
Hyptis crenata	Brazil	Leaves	Infusion	Sinusitis, fever	Ribeiro et al. (2017)
	Brazil	Roots	Infusion	Contraceptive	Elisabetsky and Posey (1989)
	Brazil	Roots	Infusion	General pains, bad cold, rheumatism, menstrual colic	Di Stasi et al. (2002)
	Brazil	Leaves	Decoction	Analgesic	Di Stasi et al. (2002)
	Brazil	Whole plant	Infusion	Menstrual regulation	Di Stasi et al. (2002)
	Brazil	Leaves	Infusion	Gastrointestinal disorders	de Jesus et al., 2009
	Brazil	Roots	Infusion	Vermifuge	Oliveira et al. (2011)
	Brazil	Leaves	Infusion	Inflammation	van den Berg and da Silva (1988)
	Brazil	Roots	Decoction; infusion	Using during pregnancy	Elisabetsky and Posey (1989)
***Hyptis* sp.**	Brazil	Leaves	n.d.	Asthma, dizzy spells, nausea, bronchitis, pains, digestive, tranquilizer, baby colic, constipation	de Albuquerque et al. (2007)
	Brazil	Leaves	n.d.	Washing post-partum	Amorozo and Gély (1988)

(continued on next page)

Table 1 (*continued*)

Species	Country regions	Part of the plant	Preparation	Ethnobotanical uses	References
Hyptis hirsuta	Brazil	n.d.	Infusion	Diabetes, stomach, flu, cough, and worms	Bieski et al. (2012)
Hyptis lacustris	Peru	Leaves	Topical application	Wounds, leishmaniasis, ring worm	Céline et al. (2009)
Hyptis lanceolata	Suriname	n.d.	n.d.	Cold	van't Klooster et al. (2016)
Hyptis obtusiflora	Peru	Leaves	Topical application	Wounds, leishmaniasis, ring worm	Céline et al. (2009)
	Ecuador		Juice	Wound healing	de la Torre et al. (2008)
	Ecuador		Infusions	Hot baths	de la Torre et al. (2008)
	Ecuador	Whole plant	Ashes	Wound healing in the legs	de la Torre et al. (2008)
	Ecuador	Leaves	Infusion	Flu and skin infections	de la Torre et al. (2008)
	Ecuador	Leaves	Maceration	Stomach pain	de la Torre et al. (2008)
	Ecuador	Leaves	Juice	To treat stings, pimples, or injuries that insects cause, especially in the most vulnerable individuals of the population	Luzuriaga-Quichimbo et al. (2018)
Hyptis paludosa	Brazil	n.d.	Infusion	Cold	Bieski et al. (2012)
***Hyptidendron canum* (syn. *Hyptis cana*)**	Brazil	Leaves	Decoction	Abortive	Rodrigues (2007)
	Brazil	Leaves; whole plant	Infusion, maceration	Diarrhea, general infection, worms, insomnia, flu, rheumatism, pains, fever	Ribeiro et al. (2017)
	Brazil	Leaves	n.d.	Anti-hemorragic, post-partum. Contraindicated in pregnancy	Vieira and Martins, 2000; Rodrigues, 2007
***Eplingiella fruticosa* (syn. *Hyptis fruticosa*)**	nd	nf	nd	Analgesic and anticonvulsant	Menezes et al., (2007); Franco et al., (2011a)
	Brazil	Fruits and leaves	Infusion Smoked cigarettes are used in asthma cases	Flu, colds and respiratory diseases	Agra et al. (2008)
***Medusantha martiusii* (syn. *Hyptis martiusii*)**	Brazil	Leaves	nd	Antifungal	Santos et al. (2013)
	Brazil	Leaves	Decoction or infusion	Intestinal and stomachic diseases	Agra et al. (2008)
	Brazil	Roots	Decoction	Ovarian inflammations	Agra et al. (2008)
***Leptohyptis macrosthachys* (syn. *Hyptis macrosthachys*)**	Brazil	Leaves	Infusion	Against asthmas, coughs and bronchitis	Agra et al. (2008)
Hypenia salzmannii	Brazil	Leaves	Decoction; infusion	Against flu, colds and respiratory diseases	Agra et al., (2007; 2008)
	Brazil	Leaves	n.d.	Cough, influenza, colds, respiratory problems in general	de Albuquerque et al. (2007)
	n.d.	n.d.	n.d.	Diseases of the respiratory tract	Falcão et al. (2003)
Marsypianthes chamaedrys	Brazil	Leaves, whole plant	Infusion	Carminative and digestive	Agra et al., (2007; 2008)
	Brazil	Leaves, whole plant	n.d.	Cough, bronchitis, flatulence, fever, articular rheumatism, antiophidic, stimulant, digestive	
	Brazil	Leaves	Maceration	Snake bite *Bothrops jararaca*	de Moura et al. (2015)
	Brazil	Leaves	Decoction, infusion	Asthma, stomachache, gastritis, ulcer, vaginal discharge, uterine and ovarian inflammation, wound healing	Ribeiro et al. (2017)
	n.d	Whole plant	nd	Snake bites	de Albuquerque et al. (2007)
Rhaphiodon echinus	Brazil	Leaves, roots	n.d.	Uterine inflammation	de Albuquerque et al. (2007)

n.d. not determined.
[a] Fright" is an English-speaking Caribbean term for an ethnomedicinal condition of persistent distress.

(**23**), sugiol (**24**), 7-α-acetoxyroyleanone (**25**), royleanone (**26**), 7-ketoroyleanone (**27**), 7α-ethoxyroyleanone (**28**), iguestol (**29**), deoxyneocryptotanshinone (**30**), 12-hydroxy-11-methoxyabieta-8,11,13-trien-7-one (**31**), cryptojaponol (**32**) and orthosiphonol (**33**) (Fronza et al., 2011).

The species *Condea undulata* (Schrank) Harley & J.F.B.Pastore (syn. *Hyptis fasciculata* Benth.) accumulates labdane diterpenes, such as 15β-methoxyfaciculatin (**34**), 15α-methoxyfaciculatin B (**35**) and methoxynepetaefolin (**36**) (Ohsaki et al., 2005). The roots of *Condea verticillata* (syn. *Hyptis verticillata*) afforded seven abietane type diterpenoids, identified as 7-acetyl-12 methoxyhorminone (**37**), 7 -acetoxy-16-benzoxy-12-hydroxyabieta-8,12-diene-11,14-dione (**38**), 11,14 dihydroxy-12-methoxy-8,11,13-triene-7-one (**39**), 11, 14-dihydroxy-12-methoxy–18(4→3βH)*abeo*-abieta-4(19),8,11,13-tetraene-7-one (**40**), 7-acetoxy-12-methoxyabieta-8,12-diene-11,14-dione (**41**), 7,6-dehydroroyleanone (**42**), 7-acetoxyhorminone (**43**) (Bakir et al., 2006; Porter et al., 2009).

Afterwards, *Medusantha martiusii* (Benth.) Harley & J.F.B.Pastore (syn. *Hyptis martiusii* Benth.) afforded carnosol (**14**), 11,14-dihydroxy-8,11,13-abietatrien-7-one (**44**) (Costa-Lotufo et al., 2004), 7-seco-7 (20), 11(20)-diepoxy-7,14-dihydroxyabieta-8,11,13-triene (**45**), 12-methoxycarnosic acid (**46**), martiusane (**47**) (Araújo et al., 2004), 7β-hydroxy-11,14-dioxoabieta-8,12-diene (**48**) and 7α-acetoxy-12-hydroxy-1,14-dioxoabieta-8,12-diene (**49**) (Araújo et al., 2006). Phytochemical study of *Medusantha carvalhoi* (Harley) Harley & J.F.B.Pastore (syn. *Hyptis carvalhoi* Harley) led to the isolation of the abietanes rosmanol (**13**), methylrosmanol (**15**), 7α-ethoxyrosmanol (**50**), galdosol (**51**) and *epi*-isorosmanol (**52**) (Lima et al., 2012).

From *Oocephalus crassifolius* (Mart. ex Benth.) Harley & J.F.B.Pastore (syn. *Hyptis crassifolia* Mart. ex. Bentham), the new compounds 11,12,15-trihydroxy-8,11,13-abietatrien-7-one (**53**), 6α,11,12,15-tetrahydroxy-8,11,13-abietatrien-7-one (**54**), 11,12,16-trihydroxy-17(15 →

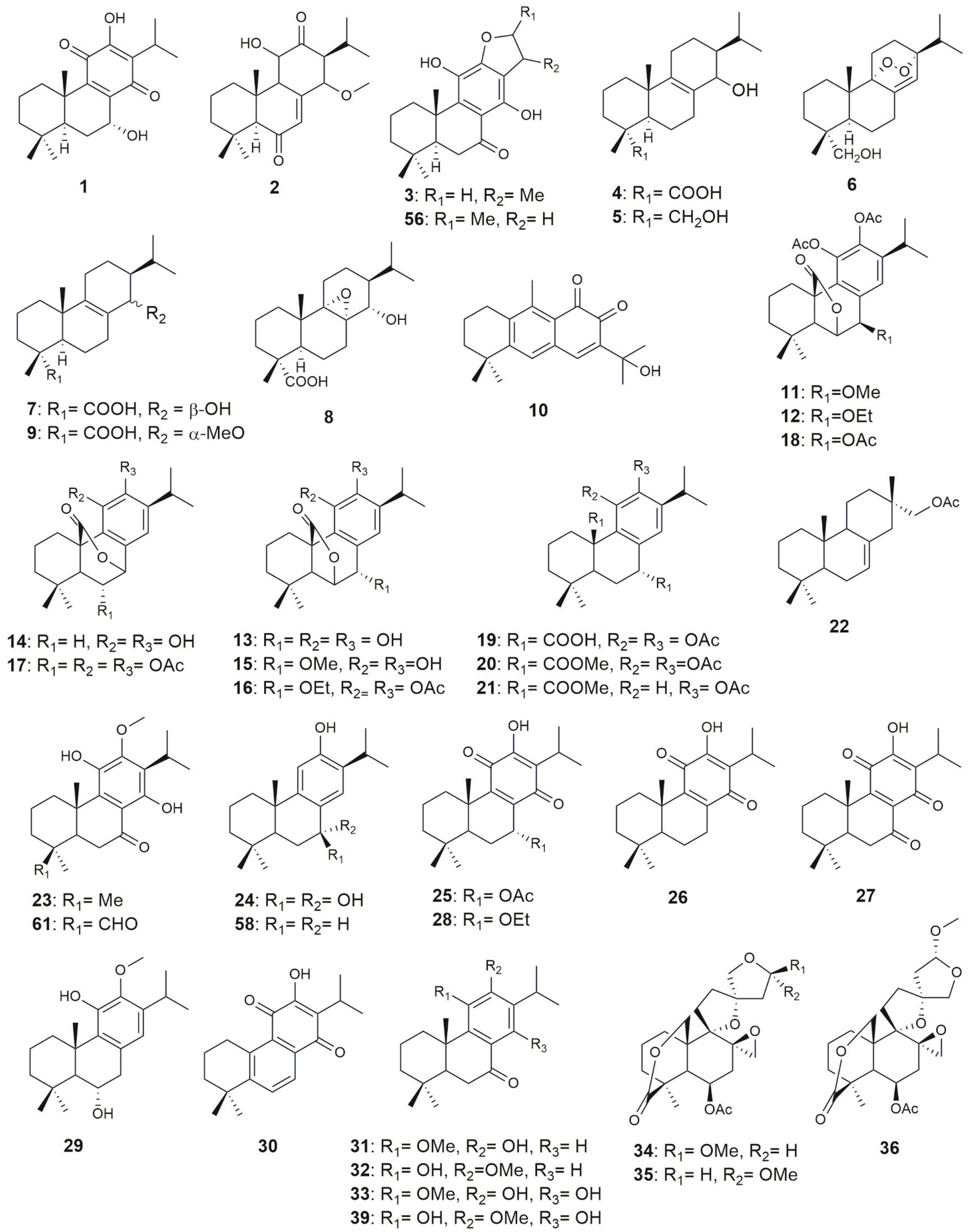

Fig. 1. Diterpenes (**1**–**57**) from Hyptidinae species.

16)-abeo-abieta-8,11,13-trien-7-one (**55**) and (16*S*)-12,16-epoxy-11,14-dihydroxy-17(15 → 16)-abeo-abieta-8,11,13-trien-7-one (**56**) were obtained. The known compounds incanone (**57**), ferruginol (**58**), sugiol (**24**), 11-oxomanoyloxide (**59**) and 11*β*-hydroxymanoyloxide (**60**) were also obtained from this plant (Lima et al., 2015).

Subsequently, the new abietanes 19-oxo-inoroyleanol (**61**), 11,14-dihydroxy-12-methoxy-7-oxo-8,11,13-abietatrien-19,20*β*-olide (**62**) and 19,20-epoxy-12-methoxy-11,14,19-trihydroxy-7-oxo-8,11,13-abietatriene (**63**), in addition to the known compounds inuroyleanol (**23**) and coulterone (**64**) were obtained from the roots of *Gymneia platanifolia* (Mart. ex Benth) Harley & J.F.B.Pastore (syn. *Hyptis platanifolia* Mart. ex. Benth.) (Araújo et al., 2005). The isopimarane diterpene, salzol (**65**) was isolated from the leaves of *Hypenia salzmannii* (Benth.) Harley & J.F.B. Pastore (syn. *Hyptis salzmannii* Benth.), respectively (Messana et al., 1990).

Bioassay-guided fractionation of extracts from *Cantinoa americana* (syn. *Hyptis spicigera*) resulted in the isolation of 19-acetoxy-2*α*,7*α*,15-trihydroxylabda-8(17),13(*Z*)-diene (**66**), 15,19-diacetoxy-2*α*,7*α*,15-dihydroxylabda-8(17),13(*Z*)-diene (**67**), 7*α*,15,19-triacetoxy-2*α*-hydroxylabda-8(17),13(*Z*)-diene (**68**), 19-acetoxy-2*α*,7*α*-dihydroxylabda-8(17),13(*Z*)-dien-15-al (**69**), 19-acetoxy-7*α*,15-dihydroxylabda-8(17),13(*Z*)-dien-2-one (**70**), 19-acetoxy-2*α*,7*α*-dihydroxylabda-14,15-

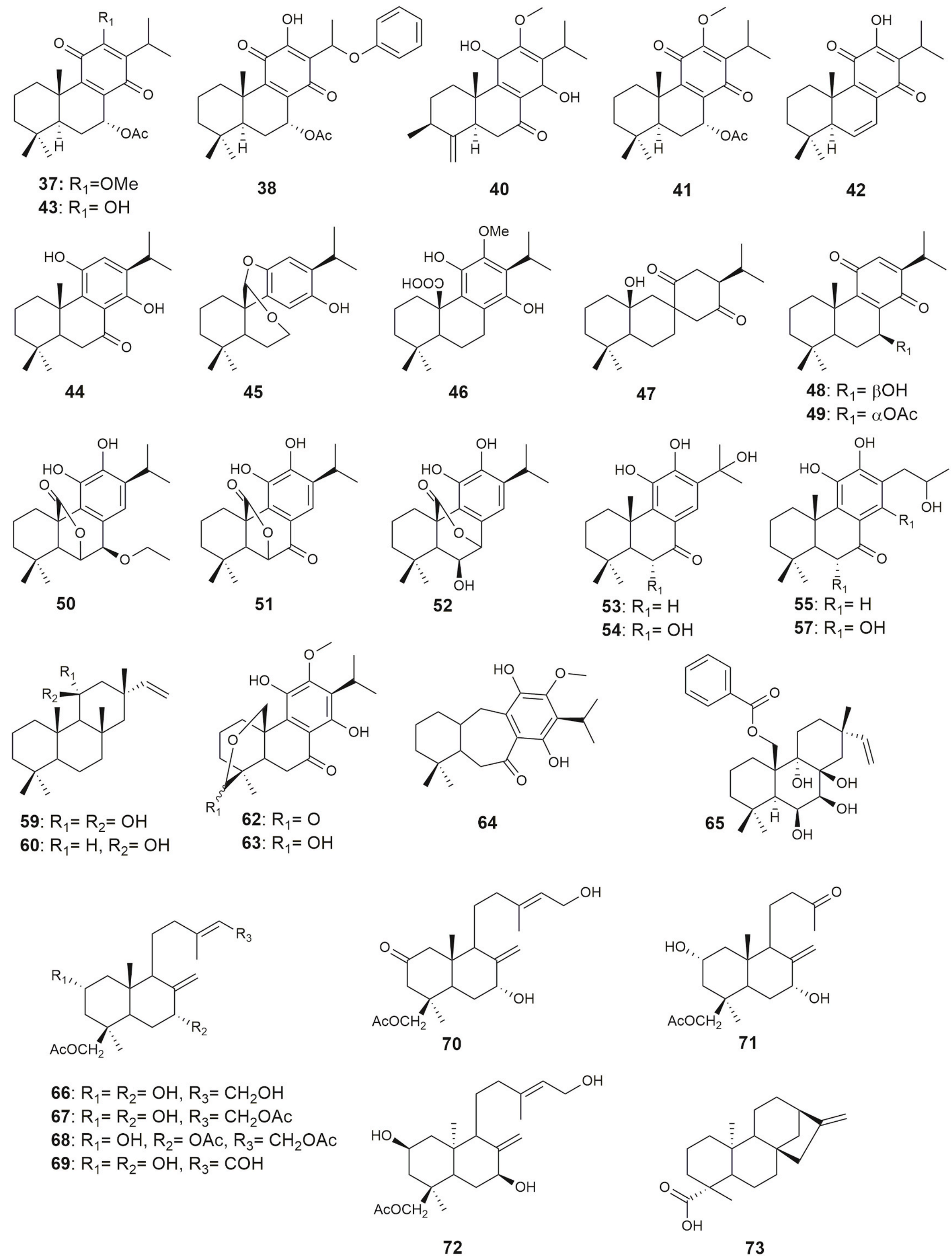

Fig. 1. (*continued*).

dinorlabd-8(17)-en-13-one (**71**) and 2α,7α,15,19-tetrahydroxy-ent-labda-8(17),13(*Z*)-diene (**72**) (Fragoso-Serrano et al., 1999).

Recently, Bridi et al., (2020) have reported the presence of *ent*-kaurane diterpenes in three *Cantinoa* species. Kaurenoic acid (**73**) was isolated from *Cantinoa heterodon* (Epling) Harley & J.F.B.Pastore (syn. *Hyptis heterodon* Epling) and characterized by GC-MS in the species *Cantinoa stricta* (Benth.) Harley & J.F.B.Pastore (syn. *Hyptis stricta* Benth.) and *Cantinoa mutabilis* (Rich.) Harley & J.F.B.Pastore (syn. *Hyptis mutabilis* Rich.). The occurrence of this type of diterpenes in Hyptidinae is rare and as far as it is known, this is the only report of the presence of *ent*-kaurane diterpenes in species from this taxon. This type of structure is more frequent in species that belongs to Asteraceae family (García et al., 2007; Villa-Ruano et al., 2016). The restricted occurrence of kaurane diterpenes in species of *Cantinoa* is interesting and other species should be studied to determine whether they could be taxonomic markers of the genus.

4.2. Triterpenes

Chemical investigations on Hyptidinae afforded, until now, forty triterpenes (Fig. 2). A series of studies carried out with *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) allowed the isolation of betulinic acid (**74**), oleanolic acid (**75**) α-peltoboykinolic acid (**76**), β-sitosterol (**77**) (Misra et al., 1981), ursolic acid (**78**), 3β-hydroxylup-20(29)-en-27-oic acid (**79**), sitosterol-β-D-glucoside (**80**) (Misra et al., 1983a). Also from this species, 3β-hydroxylup-12-en-28-oic acid (**81**), α-amyrin (**82**) and β-amyrin (**83**) were obtained (Misra et al., 1983b). In other studies, this species yielded the triterpenes urs-12-en-3-β-ol-29-oic acid (**84**) (Mukherjee et al., 1984) and hyptadienic acid (**85**) (Raja Rao et al., 1990; Prawatsri et al., 2013).

Still from the *Mesosphaerum* genus, the triterpenes ursolic acid (**78**), 2α-hydroxyursolic acid (**86**), maslinic acid (**87**), pomolic acid (**88**) and 2α,3α-dihydroxy oleanolic acid (**89**) were isolated from *Mesosphaerum oblongifolium* (Benth.) Kuntze (syn. *Hyptis oblongifolia* Benth.)

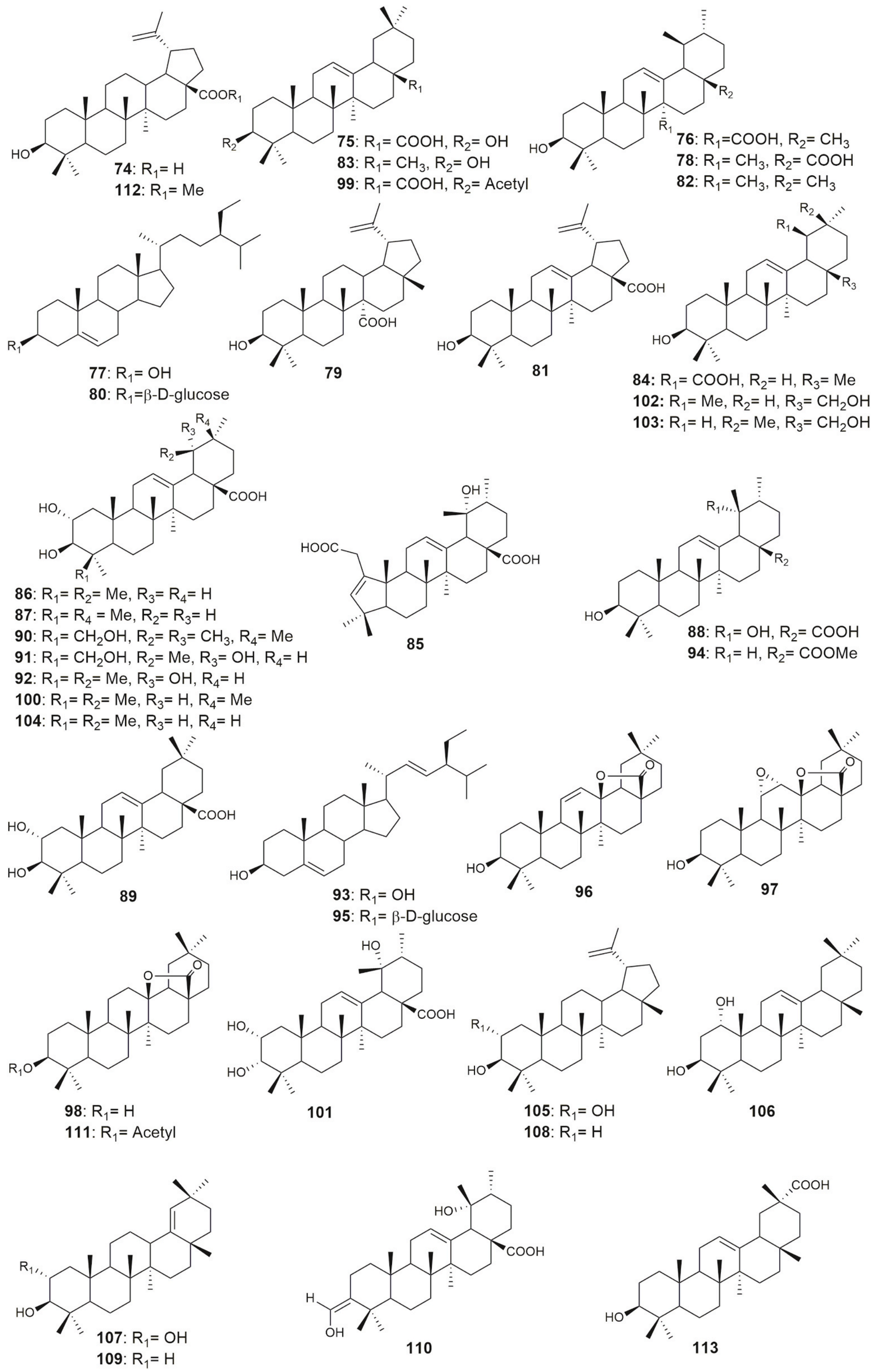

Fig. 2. Triterpenes (**58**–**85**) from Hyptidinae species.

(Pereda-Miranda et al., 1990). From the aerial parts of *Mesosphaerum urticoides* (Kunth.) Harley & J.F.B.Pastore (syn. *Hyptis urticoides* Kunth.), ursolic acid (**78**) was isolated (de Vivar et al., 1991).

Bioassay-guided fractionation of a methanolic extract from *Hyptis capitata* Jacq. yielded two new triterpene acids, named hyptatic acids A (**90**) and B (**91**), along with the known ones 2*α*-hydroxyursolic acid (**86**), maslinic acid (**87**) and tormentic acid (**92**) (Yamagishi et al., 1988). Other study led to the isolation of oleanolic acid (**75**), ursolic acid (**78**) and stigmasterol (**93**) from the same species (Almtorp et al., 1991; Kashiwada et al., 1998; Lee et al., 1988). From *Hyptis brevipes* Poit., three triterpenes, ursolic acid (**78**), sitosterol-*β*-D-glucoside (**80**) and maslinic acid (**87**) were obtained (Deng et al., 2009). The ethanolic extracts of *Hyptis radicans* (Pohl.) Harley & J.F.B. Pastore (syn. *Peltodon radicans* Pohl.) afforded *β*-sitosterol (**77**), ursolic acid (**78**), sitosterol-*β*-D-glucoside (**80**), *α*-amyrin (**82**), β-amyrin (**83**), tormentic acid (**92**), stigmasterol (**93**), 3*β*-hydroxy-28-methyl-ursulate (**94**) and stigmasterol-*β*-D-glucoside (**95**) (da Costa et al., 2008).

The triterpene betulinic acid (**74**) was isolated from the flowering aerial parts of *Condea emoryi* (Torrey.) Harley & J.F.B.Pastore (syn. *Hyptis emoryi* Torr.) (Sheth et al., 1972). Chemical investigation of the aerial parts of *Condea albida* (Kunth.) Harley & J.F.B.Pastore (syn. *Hyptis albida* Kunth.) resulted in the isolation of triterpene lactones 3*β*-hydroxyolean-28,13*β*-olide (**96**), 3*β*-hydroxy-11*α*, 12*α*-epoxyolean-28,13*β*-olide (**97**), 3*β*-hydroxyolean-11-en-28,13*β*-olide (**98**), in addition to the known compounds oleanolic acid acetate (**99**), betulinic acid (**74**), oleanolic acid (**75**) and ursolic acid (**78**) (Pereda-Miranda and Delgado, 1990). The hexanic extract from the aerial parts of *Condea undulata* (syn. *Hyptis fasciculata*) afforded betulinic acid (**74**), oleanolic acid (**75**), *β*-sitosterol (**77**), ursolic acid (**78**) and stigmasterol (**93**) (Falcão et al., 2003).

From the stems of *Hyptidendron canum* (Pohl. ex Benth.) R. Harley, a series of triterpenes were isolated. The compounds were identified as betulinic acid (**74**), *β*-sitosterol (**77**), ursolic acid (**78**), sitosterol-*β*-D-glucoside (**80**), *α*-amyrin (**82**), *β*-amyrin (**83**), maslinic acid (**87**), stigmasterol (**93**), 2*α*-3*β*-dihydroxyursolic acid (**100**), eucasphic acid (**101**), uvaol (**102**) and eritrodiol (**103**) (Lemes et al., 2011). The species *Marsypianthes chamaedrys* (Vahl.) Kuntze biosynthesizes several triterpenes, such as the novel compound chamaedrydiol (**104**), and the known ones α-amyrin (**82**), β-amyrin (**83**), lup-29(29)-ene-2α-3β-diol (**105**), castanopsol (**106**), epigermanidiol (**107**), lupeol (**108**) and germanicol (**109**) (de Sousa Menezes et al., 1998).

From *Cantinoa mutabilis* (syn. *Hyptis mutabilis*), two new triterpenes, 3*α*,19*α*-dihydroxyurs-12-en-28-oic- acid (**110**), 3*β*-acetoxy-oleanan-13*β*,28-olide (**111**), besides the known ones oleanolic acid (**75**), ursolic acid (**78**), maslinic acid (**87**), oleanolic acid acetate (**99**) and methyl betulinate (**112**) were obtained (Pereda-Miranda and Gascón-Figueroa, 1988). A study was published reporting the isolation of oleanolic acid (**75**), sitosterol-*β*-D-glucoside (**80**), tormentic acid (**92**) and 2*α*-3*β*-dihydroxyursolic acid (**100**) from *Eriope blanchetii* (Benth.) Harley (David et al., 2001). Still addressing the genus *Eriope*, the species *Eriope latifolia* (Mart. ex Benth.) Harley can accumulate oleanolic acid (**75**), ursolic acid (**78**) and epikatonic acid (**113**) (Santos et al., 2011). Finally, the ethyl acetate fraction from *Hypenia salzmannii* afforded betulinic acid (**74**), oleanolic acid (**75**), ursolic acid (**78**) and sitosterol-*β*-D-glucoside (**80**) (de Lucena et al., 2013).

4.3. Lignans

Lignans are important active metabolites found in several species from the subtribe Hyptidinae, especially *Condea verticillata* (syn. *Hyptis verticillata*) which afforded 20 different compounds. Their chemical structures are shown in Fig. 3. A study published in 1971, reported the isolation of 4′-demethyldeoxypodophyllotoxin (**114**) and *β*-peltatin (**115**) (German, 1971). Subsequently, a chemical prospection developed by Novelo et al. (1993) led to the isolation of 4′-demethyldeoxypodophyllotoxin (**114**), 5-methoxydehydropodophyllotoxin (**116**), dehydro-*β*-peltatin methyl ether (**117**), dehydropodophyllotoxin (**118**) deoxydehydropodophyllotoxin (**119**), yatein (**120**), isodeoxypodophyllotoxin (**121**), deoxypicropodophyllin (**122**) and *β*-apopicropodophyllin (**123**). Further studies with the same plant afforded podophyllotoxin (**124**), hyptinin (**125**), podorhizol (**126**), epipodorhizol (**127**) (Kuhnt et al., 1994), hyptoside (**128**) and deoxypicropodophyllin (**129**) (Hamada et al., 2012). More recently, *β*-peltatin-6-*O*-glucoside (**130**), 4′-demethyl-deoxypodophyllotoxin-4′-*O*-glucoside (**131**), 4′-*O*-demethyldehydrodeoxy podophyllotoxin (**132**) and deoxypodophyllotoxin (**133**), besides the previously reported lignans **114**, **115**, **118**, **119**, **120**, **123**, **124** were isolated from the species (Fragoso-Serrano and Pereda-Miranda, 2020).

In addition to *Condea verticillata*, other species from the genus also afforded lignans. The compounds deoxypodophyllotoxin (**133**) and sesamin (**134**) were isolated from the flowering aerial parts of *Condea tomentosa* (Poit.) Harley & J.F.B.Pastore (syn. *Hyptis tomentosa* Poit.). The latter compound (**134**) was also obtained from *Condea undulata* (syn. *Hyptis fasciculata*) (Falcão et al., 2003).

The bioguided fractionation of the aerial parts of *Hyptis rhomboidea* M. Martens & Galeotti allowed the identification of seven new lignans named hyprhombin A - E (**135** - **139**), epihyprhombin B (**140**) and hyprhombin B methyl ester (**141**) (Tsai and Lee, 2014). In another study, the aerial parts from *Hyptis capitata* afforded the lignan 2,3-di(3′, 4′-methylenedioxybenzyl)-2-buten-4-olide (**142**) (Almtorp et al., 1991). The roots of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) accumulate podophyllotoxin (**124**) and picropodophyllotoxin (**143**) (Tang et al., 2019).

From *Hypenia salzmannii* (syn. *Hyptis salzmannii*), a study describes the isolation of sesamin (**134**), cubebin (**144**) and hinokinin (**145**) (Messana et al., 1990). Subsequently, from the same species, hypenol (**146**), a new lignan, was identified along with the known *β*-peltatin-A methyl ether (**147**)(de Lucena et al., 2013).

Some species of *Eriope* also produce lignans. Raffauf et al. (1987) reported the isolation of *β*-peltatin (**115**) and *α*-peltatin (**148**) from *Eriope macrostachya* Mart. ex Benth. Further studies led to the identification of *β*-peltatin (**115**), yatein (**120**), podophyllotoxin (**124**) and *α*-peltatin (**148**) in the aerial parts of *Eriope blanchetii* (David et al., 2001) and *Eriope latifolia* (Santos et al., 2011).

Lignans are divided into several subgroups including arylnaphthalene, aryltetralin, dibenzylbutane, dibenzylbutyrolactone, and furofuran (Simpson and Amos, 2017). Among the classes, the aryltetralins have attracted significant interest, in particular, podophyllotoxin (**124**). This compound exhibits a remarkable anti-cancer effect and is the precursor of the semisynthetic anticancer drugs teniposide and etoposide.

Podophyllotoxin has been commercially obtained from the rhizomes and roots of Podophyllum spp. Strategies have been outlined to find alternative sources of this compound from plants and *in vitro* cultures of several species. In this context, in order to search for lignans, a liquid chromatography–mass spectrometry (LC-MS) method was developed and allowed the detection of compounds such as *β*-peltatin (**115**), yatein (**120**), podophyllotoxin (**124**) and *α*-peltatin (**148**) in five species of Hyptidinae (*Leptohyptis calida* (Mart. ex Benth.) Harley & J.F.B.Pastore; *Leptohyptis macrostachys* (Benth.) Harley & J.F.B.Pastore; *Eriope hypenioides* Mart. ex Benth.; *Eriope exaltata* Harley and *Oocephalus crassifolius*) (Brandão et al., 2017). Moreover, recently, an ultra - high - performance liquid chromatography - photodiode array - high resolution electrospray ionization tandem mass spectrometry (UHPLC - PDA - HRESI - MS/MS) method, aiming at to dereplicate podophyllotoxin-type lignans in *Condea verticillata* (syn. *Hyptis verticillata*) has also been proposed (Fragoso-Serrano and Pereda-Miranda, 2020). Besides that, efforts to obtain podophyllotoxin from tissue culture of Hyptidinae species have been successfully carried out. The *in vitro* propagation of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) (Bazaldúa et al., 2019; Velóz et al., 2013) and *Leptohyptis macrostachys* (Meira et al., 2017) reached the goal, resulting in an increase in the production of podophyllotoxin (**117**) and yatein (**113**), in relation to the wild plants.

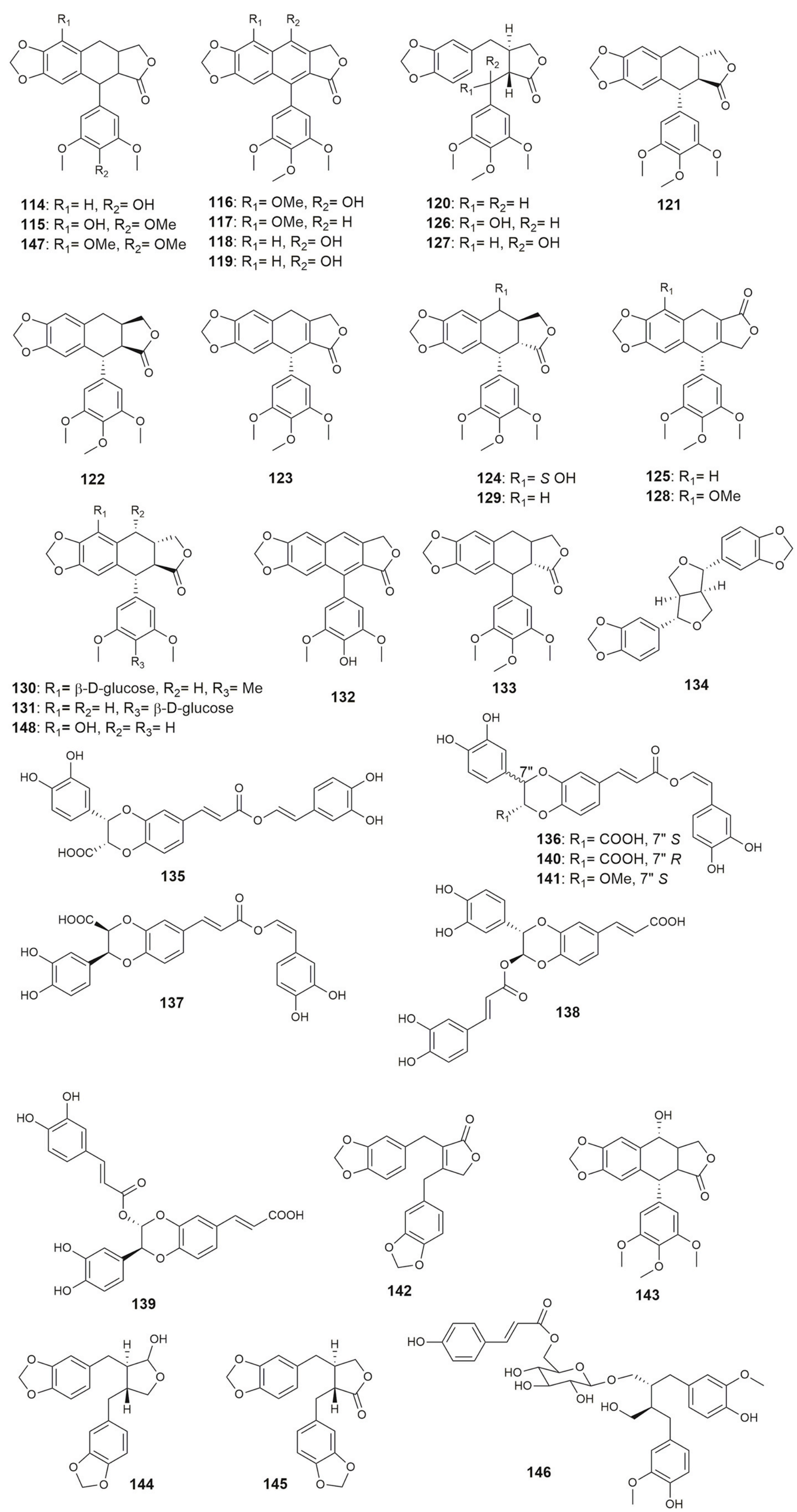

Fig. 3. Lignans (**86–113**) from Hyptidinae species.

4.4. α-pyrones

Hyptolide (**149**) was the first α-pyrone isolated from Hyptidinae (Fig. 4). The compound was obtained from *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) in 1920 (Gorter, 1920), but its structure was completely elucidated only in 1964 (Birch and Butler, 1964). Further studies were developed with this species, allowing the isolation of pectinolides A – C (**150**–**152**) (Pereda-Miranda et al., 1993) and D – H (**153**–**157**) (Boalino et al., 2003; Fragoso-Serrano et al., 2005). Recently, five α-pyrones were isolated from the same species and named as pectinolides I – M (**158**–**162**) (Martínez-Fructuoso et al., 2019).

Studies with *Mesosphaerum oblongifolium* (syn. *Hyptis oblongifolia*) led to the isolation of four new compounds of this class, 4-deacetoxy-10-*epi*-olguine (**163**), 6*R*-[5*R*,6*S*-(diacetyloxy)-1*R*-(hydroxy)-2*R*-(methoxy)-3*E*-heptenyl]-5,6-dihydro-2H-pyran-2-one (**164**), 6*R*-[5*R*,6*S*-(diacetyloxy)-1*S*,2*R)*-(dihydroxy)-3*E*-heptenyl]-5,6-dihydro-2H-pyran-2-one (**165**) and 6*R*-[1*R*,2*R*,5*R*,6*S*-(tetracetyloxy)-3*E*-heptenyl-5,6-dihydro-2H-pyran-2-one (**166**) (Pereda-Miranda and Delgado, 1990). From *Mesosphaerum urticoides* (syn. *Hyptis urticoides*) the compound hypurticin (**167**) was isolated (de Vivar et al., 1991).

A study published in 1979 reports the isolation of the compounds anamarine (**168**) and olguine (**169**), obtained from an unidentified

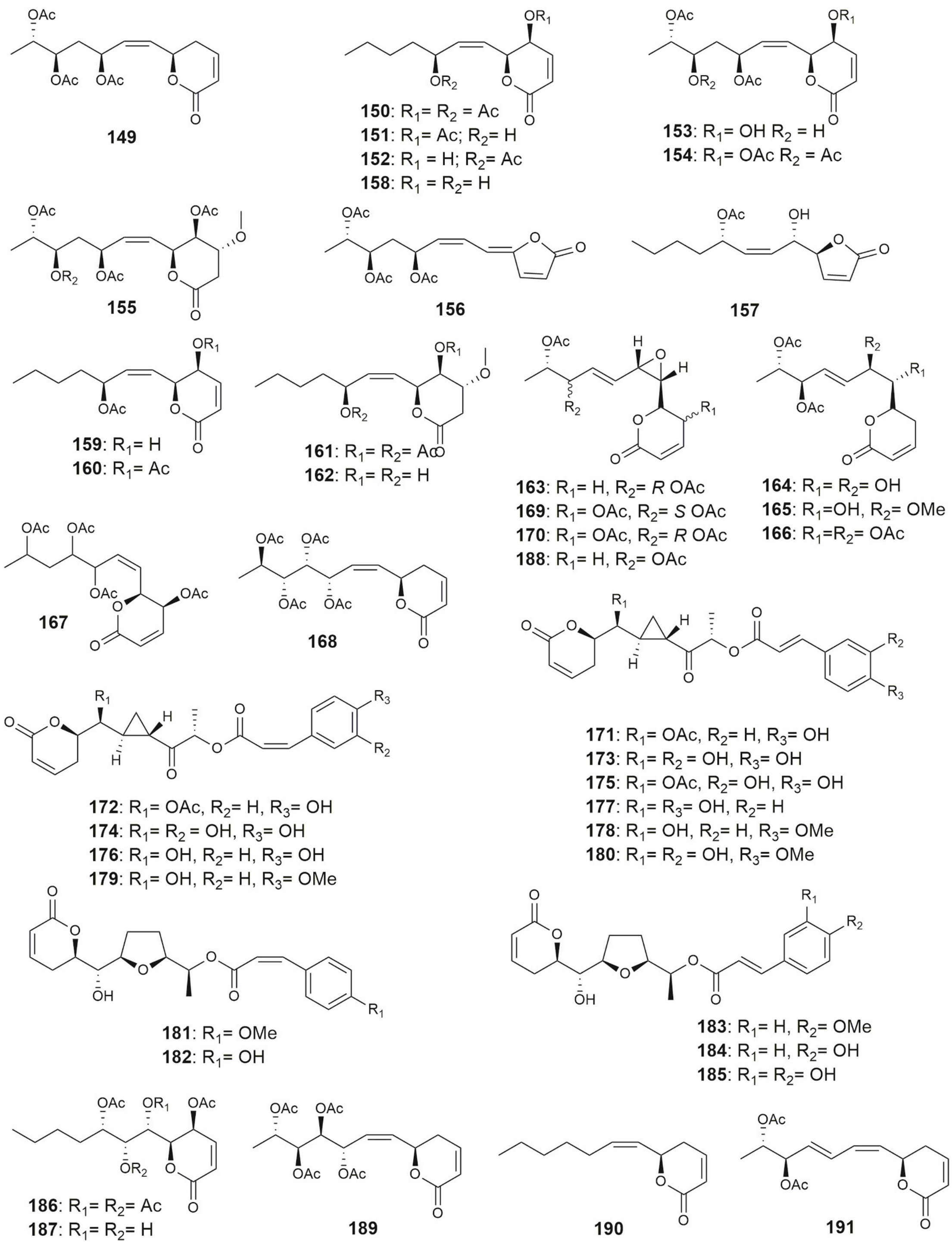

Fig. 4. α-pyrones (**114**–**146**) from Hyptidinae species.

species of *Hyptis* (Alemany et al., 1979). The compound 10-*epi*-olguine (**170**) was isolated from the aerial parts of *Hyptis capitata.* This compound is structurally similar to hypurticin (**167**) that presents an acetoxy group linked to the lactone pyran ring (Almtorp et al., 1991). Later, a series of chemical studies carried out with *Hyptis brevipes* led to the identification of fifteen new α-pyrones named brevipolides A – F (**171**–**176**) (Deng et al., 2009), G – J (**177**–**180**) (Suárez-Ortiz et al., 2013) and K – O (**181**–**185**) (Suárez-Ortiz et al., 2017). Additionally, the compounds named monticolides A (**186**) and B (**187**) were obtained from *Hyptis monticola* Mart. ex. Benth. (Martínez-Fructuoso et al., 2019).

Two α-pyrones were obtained from *Cantinoa americana* (syn. *Hyptis spicigera*) and named spicigera-α-lactone (**188**) and spicigerolide (**189**) (Aycard et al., 1993; Pereda-Miranda et al., 2001). The volatile fraction of *Gymneia interrupta* (Pohl ex Benth.) Harley & J.F.B.Pastore (syn. *Hyptis ovalifolia* Bentham) presented (*R*)-6-[1-heptenyl]-5,6-dihydro-2*H*-pyran (**190**) as the main compound (Souza et al., 2003) and the aerial parts of *Leptohyptis macrostachys* (Benth.) Harley & J.F.B.Pastore (syn. *Hyptis macrostachys* Benth in DC.) afforded the α-pyrone hyptenolide (**191**) (Costa et al., 2014).

4.5. Flavonoids

Thirty flavonoids were identified, being flavones the class most frequently found (Fig. 5). In 1979, the compounds 5-hydroxy-4′,6,7,8-tetramethoxyflavone (**192**), 5-hydroxy-4′,3,6,7,8-pentamethoxyflavone (**193**), 5-hydroxy-3′,4′,6,7-tetramethoxy-flavone (**194**) and eupatorin (**195**) were isolated from *Condea tomentosa* (syn. *Hyptis tomentosa*) (Kingston et al., 1979). Phytochemical investigations of the polar fractions of *Condea albida* (syn. *Hyptis albida*) led to the isolation of apigenin-7,4′-dimethyl ether (**196**), nevadensin A (**197**), gardenin B (**198**), kaempferol-3,7,4′-trimethyl ether (**199**) and ermanin (**200**) (Pereda-Miranda and Delgado, 1990). Subsequently, *Condea verticillata* (syn.

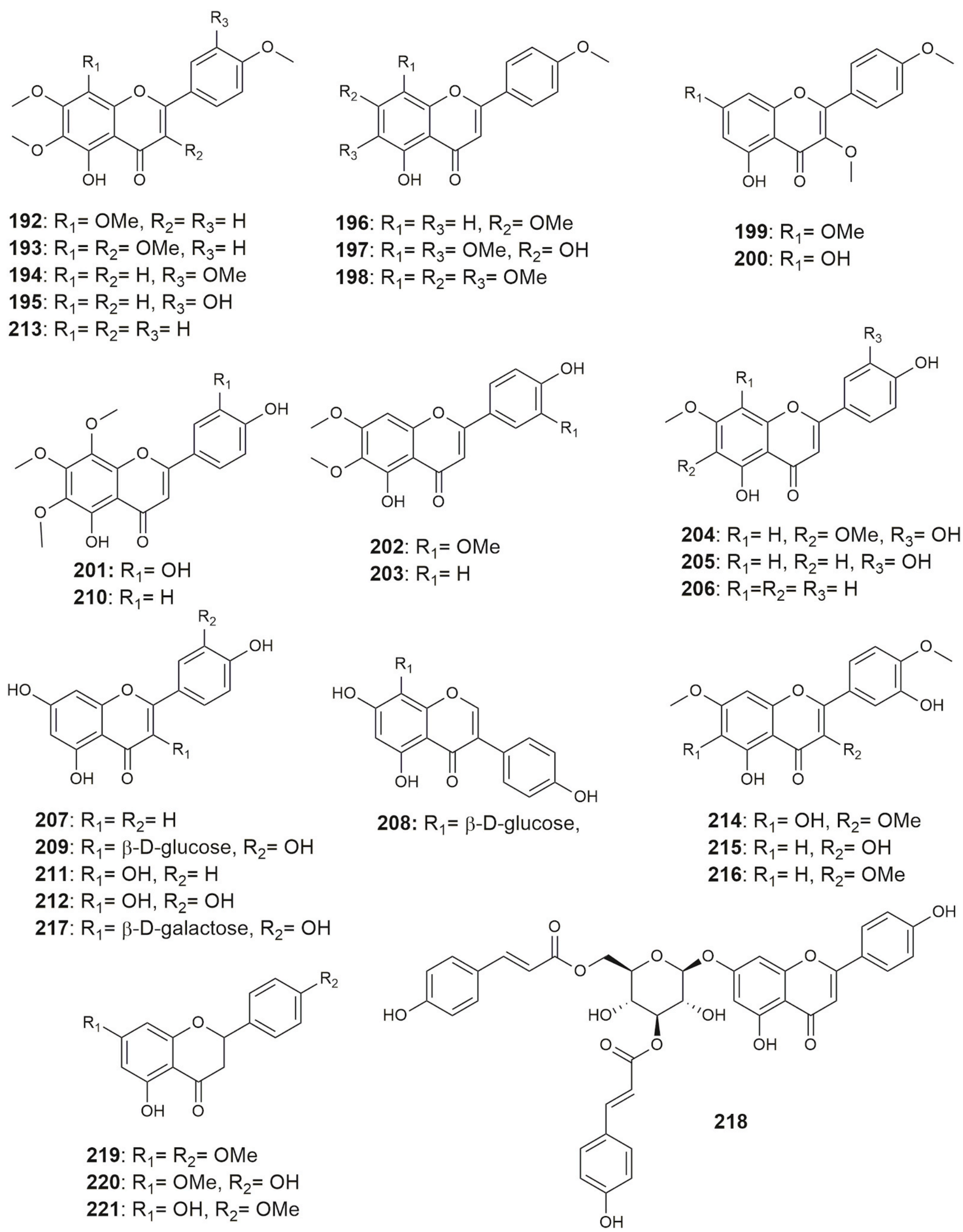

Fig. 5. Flavonoids (**147**–**173**) from Hyptidinae species.

Hyptis verticillata) afforded the flavonoid sideritoflavone (**201**) (Kuhnt et al., 1994) and, more recently, from *Condea undulata* (syn. *Hyptis fasciculata*) the methoxylated flavones cirsilineol (**202**) and cirsimaritin (**203**) were isolated (Isobe et al., 2006).

Fractionation of the ethanolic extract of *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) resulted in the isolation of cirsiliol (**204**), 7-*O*-methyl-luteolin (**205**), genkwanin (**206**) and cirsimaritin (**203**) (Falcão et al., 2013). The aerial parts of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) afforded genkwanin (**206**), apigenin (**207**), genistein-8-*C*--glucoside (**208**), quercetin-3-*O*-glucoside (**209**) sorbifolin (**210**), kaempferol (**211**) and quercetin (**212**)(Prawatsri et al., 2013; Tang et al., 2019). The methoxylated flavone salvigenin (**213**) was isolated from *Mesosphaerum urticoides* (syn. *Hyptis urticoides*) (de Vivar et al., 1991).

Species from the genus *Hyptis* also afforded flavones and flavonols. The compound apigenin-7,4′-dimethyl ether (**196**) was isolated from *Hyptis capitata* (Almtorp et al., 1991) and further methoxylated flavones, the compounds 5,6,3′-trihydroxy-3,7,4′-trimethoxyflavone (**214**), 3,5, 3′-trihydroxy-7,4′-dimethoxy flavone (**215**) and 5,3′-dihydroxy-3,7, 4′-trimethoxyflavone (**216**), were obtained from *Hyptis brevipes* (Deng et al., 2009). *Hyptis atrorubens* Poit. was reported to contain isoquercetin (**209**) and hyperoside (**217**) (Abedini et al., 2013). Subsequently, a study conducted with *Hyptis rhomboidea* identified the flavones apigenin (**207**) and anisofolin A (**218**), as well as the flavonols kaempferol (**211**) and quercetin (**212**) (Tsai and Lee, 2014).

Studies carried out with the polar extracts of *Hypenia salzmannii* (syn. *Hyptis salzmannii*) allowed the identification of the flavonoid hyperoside (**217**) and the flavanones naringenin-7,4-dimethylether (**219**), sakuranetin (**220**) and isosakuranetin (**221**) (Messana et al., 1990; de Lucena et al., 2013). Finally, the flavone salvigenin (**213**) was also isolated from *Hyptidendron canum* (Lemes et al., 2011).

4.6. Phenolic acids

Phenolic acids are accumulated in several species. Until now, fifteen compounds of this class were found in these plants (Fig. 6).

The leaves of *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) afforded a series of phenolic acids identified as rosmarinic acid (**222**), 3-*O*-methyl-rosmarinic acid (**223**), ethyl caffeate (**224**), sambacaitaric acid (**225**) and 3-*O*-methyl-sambacaitaric acid (**226**), nepetoidin A (**227**) and nepetoidin B (**228**) (Falcão et al., 2013). Chemical investigations of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) allowed the identification of rosmarinic acid (**222**) and methyl rosmarinate (**229**) (Prawatsri et al., 2013; Abedini et al., 2013; Tang et al., 2019). More recently, a study carried out with the later species led to the isolation of five caffeoylquinic acid derivatives, identified as 3,5-dicaffeoylquinate (**230**), 4,5-dicaffeoylquinate (**231**), 3,4-dicaffeoylquinate (**232**), methyl-3,5- dicaffeoylquinate (**233**), methyl-3,4- dicaffeoylquinate (**234**) (Hsu et al., 2019).

Rosmarinic acid (**222**) was identified in the aerial parts of *Hyptis capitata* (Almtorp et al., 1991). The same compound (**222**), in addition to methyl rosmarinate (**229**), was obtained from *Hyptis atrorubens* (Abedini et al., 2013). The species *Condea verticillata* (syn. *Hyptis verticillata*) also afforded the compound rosmarinic acid (**222**) (Kuhnt et al., 1994). A study developed with stems of *Condea undulata* (syn. *Hyptis fasciculata*) led to the identification of caffeic acid (**235**) (Falcão et al., 2003). Finally, from *Hypenia salzmannii* (syn. *Hyptis salzmannii*) the phenolic acids rosmarinic acid (**222**), methyl rosmarinate (**229**) and *p*-methoxycinnamic acid (**236**) were obtained (de Lucena et al., 2013; Messana et al., 1990).

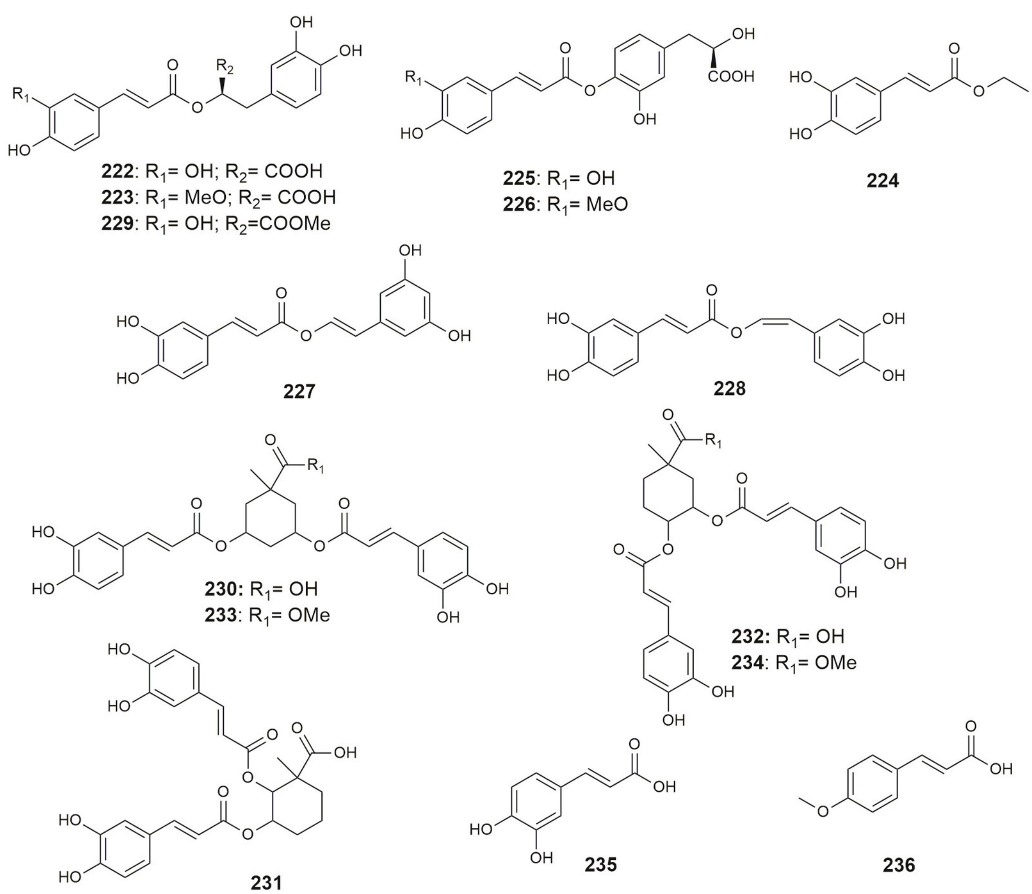

Fig. 6. Phenolic acids (**174–182**) from Hyptidinae species.

4.7. Essential oils

Most genera of Hyptidinae include aromatic species that have been attracting interest from researchers for a long time. The first study found on essential oils of a species of this taxon dates from 1935, and deals with the obtaining of essential oil from *Cantinoa mutabilis* (syn. *Hyptis mutabilis*) (Werner, 1935). Subsequently, since the 1980s, a number of articles have been published, focusing on obtaining essential oils from several species, both from the fresh or dried leaves. The main compounds (>5%) present in the composition of these oils are summarized in Table 2 and their molecular structures are shown in Fig. 7.

Several studies regarding the composition of the essential oil from *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) were published up to the present time (Table 2). The specimens were collected in different parts of the world including Australia, Brazil, Cameroon, Cuba, China, El Salvador, Guinea-Bissau, India, Italy, Laos, Nigeria and Venezuela. Although the plants have different origins, the chemical composition is somewhat similar, being sabinene (**246**), 1,8-cineole (**250**) and *β*-caryophyllene (**262**) the most abundant components cited in the majority of the reports.

Six studies reported the composition of the essential oils from *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) (Tchoumbougnang et al., 2005; Arrigoni-Blank et al., 2008; Nascimento et al., 2008; Jesus et al., 2016; Feitosa-Alcantara et al., 2017; Oliveira de Souza et al., 2017). These oils presented as the major compounds the sesquiterpene hydrocarbons, *β*-caryophyllene (**262**), germacrene-D (**269**) and *β*-elemene (**263**). The samples collected in Brazil (five of them) afforded great amounts of caryophyllene oxide (**284**), and the sample from Cameroon did not present high levels of oxygenated sesquiterpenes. The fresh leaves of *Mesosphaerum sidifolium* afforded an essential oil (ca. 0.6%) rich in limonene (**244**), fenchone (**253**) and cubebol (**292**) (Rolim et al., 2017).

The essential oil from *Hyptis goyazensis* A.St.-Hill ex Benth (Luz et al., 1984), *Eplingiella fruticosa* (syn. *Hyptis fruticosa*) (Franco et al., 2011a, 2011b; Beserra-Filho et al., 2019) and *Hyptis crenata* (Zoghbi et al., 2002) presented *α*-pinene (**238**), *β*-pinene (**239**) and 1,8-cineole (**250**) as the major components. From Cameroon, fresh leaves from *Hyptis lanceolata* Poir. afforded an essential oil rich in *β*-pinene (**239**) and germacrene-D (**269**) (Tchoumbougnang et al., 2005). *Hyptis villosa* Pohl ex Benth produces the oxygenated sesquiterpenes *epi*-*α*-cadinol (**286**), kessane (**289**) and spathulenol (**291**) as the major components of the essential oil (Silva et al., 2013a). (*E*)-methyl-cinamate (**249**), germacrene-D (**269**) and *β*-caryophyllene (**262**) were the major components from *Hyptis monticola* (Perera et al., 2017). The essential oil of *Hyptis atrorubens* presented *α*-copaene (**259**), *β*-caryophyllene (**264**) and caryophyllene oxide (**284**) as main compounds (Kerdudo et al., 2016). The same study reported the composition of the oil from *Hyptis brevipes* and *Hyptis rhomboidea*, indicating that the major components were borneol (**251**), methyl eugenol (**254**) and *β*-caryophyllene (**262**) (Xu et al., 2013).

Studies carried out with *Cantinoa americana* (syn. *Hyptis spicigera*), demonstrated the occurrence of *α*-pinene (**238**), *β*-pinene (**239**), sabinene (**246**) and *β*-caryophyllene (**262**). Regarding the *Cantinoa mutabilis* (syn. *Hyptis mutabilis*) essential oil composition, three different studies were published so far. Some variations were observed among these samples, however, the sesquiterpenes *β*-caryophyllene (**262**), bicyclogermacrene (**264**) and globulol (**287**) were the most common components. In the essential oil from *Cantinoa carpinifolia* (Benth) Harley & J.F.B.Pastore (syn. *Hyptis carpinifolia* Benth.), 1,8-cineole (**250**) and *β*-caryophyllene (**262**) were identified (de Sá et al., 2016). Recently, the volatile oils from five species of *Cantinoa* native to South Brazil were studied. The results indicated that *Cantinoa althaeifolia* (Pohl ex. Benth.) Harley & J.F.B.Pastore produces 7-*epi*-*α*-selinene (**276**) and *γ*–himachalene (**278**) as main compounds. *Cantinoa heterodon* accumulates principally *γ*-3-carene (**242**), germacrene D (**269**) and germacrene A (**274**). The essential oils from *Cantinoa sylvularum* (A.St.-Hil. ex Benth.) Harley & J.F.B.Pastore and *Cantinoa mutabilis* presented great amounts of globulol (**287**). Additionaly, the oil from *Cantinoa stricta* was mainly composed by *β*-caryophyllene (**262**) and bicyclogermacrene (**264**) (Bridi et al., 2020).

The compounds aromadendr-1(10)-en-9-one (**281**) and cadina-4,10(15)-dien-3-dione (**282**) were obtained only from the essential oil of *Condea verticillata* (syn. *Hyptis verticillata*), being its major components (ca. 30% and 15%, respectively) (Facey et al., 2005). Borneol (**251**) and elemol (**285**) were the principal components in the oil from *Condea emoryi* (syn. *Hyptis emoryi*) (Tanowitz et al., 1984).

The species *Marsypianthes chamaedrys* produces volatile oil rich in sesquiterpene hydrocarbons, principally germacrene D (**269**), bicyclogermacrene (**264**) and *β*-caryophyllene (**262**) (Callejon et al., 2016). Another study compares the essential oil produced by *Marsypianthes chamaedrys*, *Marsypianthes burchellii* Epling, *Marsypianthes foliolosa* Benth. and *Marsypianthes montana* Benth. These species accumulate great amounts of sesquiterpenes, mainly *β*-caryophyllene (**262**), germacrene D (**269**), caryophyllene oxide (**284**) and spathulenol (**291**) (Hashimoto et al., 2014).

The species *Oocephalus oppositiflorus* (Schrank) Harley & J.F.B.Pastore (syn. *Hyptis glomerata* Mart. ex Schrank) accumulates principally *β*-caryophyllene (**262**) and *γ*-cadinene (**267**) (Silva et al., 2000). The essential oil of *Medusantha martiusii* (syn. *Hyptis martiusii*), is composed predominantly by *γ*-3-carene (**242**) and 1,8-cineole (**250**) (Caldas et al., 2014; Barbosa et al., 2017).

The volatile oil from the leaves and inflorescences of *Hyptidendrum canum* presented *β*-caryophyllene (**262**), bicyclogermacrene (**264**) and amorpha-4,7(11)-diene (**272**) as the main compounds (Fiuza et al., 2010). A further study reported the composition of the essential oil from *Hypenia salzmannii*, being the monoterpene xanthoxilin (**257**) and the oxygenated sesquiterpene *β*-caryophyllene the main components (**262**) (Oliveira de Souza et al., 2017).

The dried leaves of *Rhaphiodon echinus* (Nees & Mart.) Schauer yielded 0.12% of essential oil composed principally by bicyclogermacrene (**264**), *β*-caryophyllene (**262**), caryophyllene oxide (**284**) and spathulenol (**291**) (Duarte et al., 2016).

Several species from the subtribe Hyptidinae are recognized and popularly used due to their aromatic properties. Thus, several studies have been conducted to identify the compounds present in the essential oils of these plants. Until now, the essential oils have been obtained from at least 31 species distributed in 12 genera.

5. Biological investigations

Over the years, essential oils, extracts and isolated compounds of Hyptidinae species have been assessed for biological activities, such as pesticidal/insecticidal, antimicrobial, antinociceptive and anti-ulcer, as well as for cytotoxicity. The main outcomes will be presented in the following section.

5.1. Pesticidal and insecticidal/repellent activities

Insect pests configure one of the major problems of agriculture and human health in urban and rural environments, requiring the use of insecticides for their control. However, the indiscriminate application of these chemicals has led to many environmental problems and resistance to the available compounds has been observed in many species of insects. Resistance and the same potential hazards also arise with acaricides, widely used to control pests that affect livestock (Fierascu et al., 2019). Thus, research on new pesticides with a lower toxicity to humans, cattle and wildlife, as well as beneficial insects is highly needed.

In this context, many compounds, synthetic and natural, have been investigated. In the search for active natural products, emphasis has been given to species of the Lamiaceae family. Indeed, a large number of species in this family have shown activity against a variety of pests (Boulogne et al., 2012). In most cases, the effects are attributed to

Table 2
Main compounds (>5%) of the essential oils from species of Hyptidinae.

Compound	Species	Plant parts	Origin	Amount (%)	Reference
***α*-phellandrene (237)**	*Cantinoa americana*	DL	Burkina Faso	7.0	Bayala et al. (2014)
	Mesosphaerum suaveolens	FL	Laos	28.3	Ashitani et al. (2015)
	Mesosphaerum suaveolens	FL	India	22.8	Sharma et al. (2019)
***α*-pinene (238)**	*Cantinoa americana*	FL	Cameroon	27.3	Tchoumbougnang et al. (2005)
	Cantinoa americana	DF	Cameroon	28.3[a]	Noudjou et al. (2007)
	Cantinoa americana	DL	Burkina Faso	21.7	Conti et al. (2011)
	Cantinoa americana	DL	Burkina Faso	20.1	Bayala et al. (2014)
	Cantinoa heterodon	FAP	Brazil	5.20	Bridi et al. (2020)
	Condea emoryi	DL	USA	6.6	Tanowitz et al. (1984)
	Eplingiella fruticosa	FL	Brazil	12.3	Franco et al. (2011b)
	Eplingiella fruticosa	FF	Brazil	20.5	Franco et al. (2011b)
	Eplingiella fruticosa	FL	Brazil	10.4[a]	Franco et al. (2011a)
	Eplingiella fruticosa	DL	Brazil	5.74	Beserra-Filho et al. (2019)
	Hyptis crenata	DL	Brazil	18.8[a]	Zoghbi et al. (2002)
	Hyptis dilatata	FL	Brazil	11.6	Almeida et al. (2018)
	Hyptis goyazensis	DAP	Brazil	12.7	Luz et al. (1984)
	Mesosphaerum suaveolens	FL	India	10.1	Sharma et al. (2019)
***α*-thujene (239)**	*Condea emoryi*	DL	USA	7.0	Tanowitz et al. (1984)
***β*-phellandrene (240)**	*Mesosphaerum suaveolens*	FL	Laos	8.0	Ashitani et al. (2015)
***β*-pinene (241)**	*Cantinoa americana*	FL	Cameroon	10.3	Tchoumbougnang et al. (2005)
	Cantinoa americana	DL	Burkina Faso	13.8	Conti et al. (2011)
	Cantinoa americana	DL	Burkina Faso	9.2	Bayala et al. (2014)
	Cantinoa heterodon	FAP	Brazil	16.2	Bridi et al. (2020)
	Cantinoa sylvularum	FAP	Brazil	7.40	Bridi et al. (2020)
	Eplingiella fruticosa	FL	Brazil	8.6	Franco et al. (2011b)
	Eplingiella fruticosa	FF	Brazil	13.6	Franco et al. (2011b)
	Eplingiella fruticosa	FL	Brazil	8.1[a]	Franco et al. (2011a)
	Hyptis goyazensis	DAP	Brazil	8.3	Luz et al. (1984)
	Hyptis lanceolata	FL	Cameroon	40.3	Tchoumbougnang et al. (2005)
	Mesosphaerum pectinatum	DL	Brazil	7.0	Nascimento et al. (2008)
	Mesosphaerum suaveolens	DL	Burkina Faso	9.4	Conti et al. (2011)
	Oocephalus oppositiflorus	FF	Brazil	5.2	Silva et al. (2000)
***γ*-3-carene (242)**	*Cantinoa heterodon*	FAP	Brazil	19.0	Bridi et al. (2020)
	Hyptis dilatata	FL	Brazil	18.3	Almeida et al. (2018)
	Medusantha martiusii	DL	Brazil	17.4	Caldas et al. (2013)
	Medusantha martiusii	FL	Brazil	21.6	Barbosa et al. (2017)
	Medusantha martiusii	FL	Brazil	22.5	Costa et al. (2005)
	Medusantha martiusii	FAP	Brazil	22.5	Araújo et al. (2003)
***γ*-terpinene (243)**	*Cantinoa mutabilis*	DL	Brazil	16.6	Aguiar et al. (2003)
Limonene (244)	*Cantinoa americana*	FL	Cameroon	13.4	Tchoumbougnang et al. (2005)
	Cantinoa stricta	FAP	Brazil	5.0	Bridi et al. (2020)
	Condea emoryi	DL	USA	5.6	Tanowitz et al. (1984)
	Hyptis monticola	FAP	Brazil	6.6	Perera et al. (2017)
	Mesosphaerum sidifolium	FL	Brazil	5.4	Rolim et al. (2017)
	Mesosphaerum suaveolens	DAP	Brazil	18.1[a]	Oliveira et al. (2005)
	Mesosphaerum suaveolens	DL	Burkina Faso	6.0	Conti et al. (2011)
	Mesosphaerum suaveolens	FL	Laos	8.0	Ashitani et al. (2015)
	Mesosphaerum suaveolens	FL	India	8.5	Sharma et al. (2019)
***p*-cymene (245)**	*Cantinoa mutabilis*	DL	Brazil	19.3	Aguiar et al. (2003)
	Oocephalus oppositiflorus	FF	Brazil	7.8	Silva et al. (2000)
Sabinene (246)	*Cantinoa americana*	DL	Burkina Faso	17.5	Conti et al. (2011)
	Cantinoa americana	DL	Burkina Faso	10.3	Bayala et al. (2014)
	Mesosphaerum suaveolens	DAP	Brazil	7.4[a]	Azevedo et al. (2002)
	Mesosphaerum suaveolens	FL	Nigeria	21.6[a]	Eshilokun et al. (2005)
	Mesosphaerum suaveolens	DAP	Brazil	23.0[a]	Oliveira et al. (2005)
	Mesosphaerum suaveolens	FL	Cameroon	20.6	Tchoumbougnang et al. (2005)
	Mesosphaerum suaveolens	DL	Burkina Faso	27.0	Conti et al. (2011)
	Mesosphaerum suaveolens	FL	Laos	15.0	Ashitani et al. (2015)
Terpinolene (247)	*Cantinoa americana*	DL	Burkina Faso	7.3	Conti et al. (2011)
	Cantinoa mutabilis	DL	Brazil	24.7	Aguiar et al. (2003)
	Mesosphaerum suaveolens	FL	Nigeria	5.9[a]	Eshilokun et al. (2005)
	Mesosphaerum suaveolens	DL	Burkina Faso	11.9	Conti et al. (2011)
Myrcene (248)	*Cantinoa heterodon*	FAP	Brazil	10.8	Bridi et al. (2020)
(*E*)-methyl-cinnamate (249)	*Hyptis monticola*	FAP	Brazil	7.8	Perera et al. (2017)
1,8-cineol (250)	*Cantinoa carpinifolia*	DL	Brazil	50.9[a]	de Sá et al. (2016)
	Condea emoryi	DL	USA	6.9	Tanowitz et al. (1984)
	Eplingiella fruticosa	FL	Brazil	18.7	Franco et al. (2011b)
	Eplingiella fruticosa	FF	Brazil	12.4	Franco et al. (2011b)
	Eplingiella fruticosa	FL	Brazil	17.8[a]	Franco et al. (2011a)
	Eplingiella fruticosa	DL	Brazil	12.1	Beserra-Filho et al. (2019)
	Hyptis crenata	DL	Brazil	19.2[a]	Zoghbi et al. (2002)
	Hyptis goyazensis	DAP	Brazil	23.9	Luz et al. (1984)
	Medusantha martiusii	DL	Brazil	32.8	Caldas et al. (2014)
	Medusantha martiusii	FL	Brazil	34.6	Barbosa et al. (2017)

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Table 2 (*continued*)

Compound	Species	Plant parts	Origin	Amount (%)	Reference
	Medusantha martiusii	FL	Brazil	24.3	Costa et al. (2005)
	Medusantha martiusii	FAP	Brazil	24.3	Araújo et al. (2003)
	Mesosphaerum suaveolens	DAP	Brazil	30.4	Luz et al. (1984)
	Mesosphaerum suaveolens	FL	Australia	32.0	Peerzada (1997)
	Mesosphaerum suaveolens	DAP	Brazil	12.6[a]	Azevedo et al. (2002)
	Mesosphaerum suaveolens	DAP	Brazil	12.7[a]	Oliveira et al. (2005)
	Mesosphaerum suaveolens	DAP	China	10.3	Xu et al. (2013)
	Mesosphaerum suaveolens	FL	Laos	16.5	Ashitani et al. (2015)
	Mesosphaerum suaveolens	FAP	Venezuela	16.2	Tesch et al. (2015)
Borneol (251)	*Condea emoryi*	DL	USA	11.9	Tanowitz et al. (1984)
	Hyptis goyazensis	DAP	Brazil	13.0	Luz et al. (1984)
	Hyptis rhomboidea	DAP	China	6.03	Xu et al. (2013)
Camphor (252)	*Medusantha martiusii*	DL	Brazil	6.7	Caldas et al. (2014)
	Medusantha martiusii	FL	Brazil	5.17	Barbosa et al. (2017)
Fenchone (253)	*Hyptis dilatata*	FL	Brazil	33.4	Almeida et al. (2018)
	Mesosphaerum sidifolium	FL	Brazil	24.8	Rolim et al. (2017)
	Mesosphaerum suaveolens	FAP	Venezuela	17.3	Tesch et al. (2015)
Methyl eugenol (254)	*Hypenia salzmanii*	FL	Brazil	5.6	Oliveira de Souza et al. (2017)
	Hyptis brevipes	DAP	China	11.5	Xu et al. (2013)
	Hyptis rhomboidea	DAP	China	7.8	Xu et al. (2013)
3-Allyl guaiacol (255)	*Hyptis brevipes*	DAP	China	62.7	Xu et al. (2013)
Terpinen-4-ol (256)	*Mesosphaerum suaveolens*	FL	Nigeria	10.6	Eshilokun et al. (2005)
	Mesosphaerum suaveolens	FL	Cameroon	9.6	Tchoumbougnang et al. (2005)
	Mesosphaerum suaveolens	DL	Burkina Faso	5.4	Conti et al. (2011)
Thymol (257)	*Cantinoa mutabilis*	DL	Brazil	37.4	Aguiar et al. (2003)
Xanthoxilin (258)	*Hypenia salzmanii*	FL	Brazil	17.2	Oliveira de Souza et al. (2017)
***α*-copaene (259)**	*Hyptis atrorubens*	DAP	Martinique	5.5[a]	Kerdudo et al. (2016)
***α*-humulene (260)**	*Mesosphaerum pectinatum*	FL	Cameroon	6.2	Tchoumbougnang et al. (2005)
***β*-cadinene (261)**	*Hyptis rhomboidea*	DAP	China	7.11	Xu et al. (2013)
***β*-caryophyllene (262)**	*Cantinoa americana*	FL	Cameroon	20.1	Tchoumbougnang et al. (2005)
	Cantinoa americana	DF	Cameroon	8.0[a]	Noudjou et al. (2007)
	Cantinoa americana	DL	Burkina Faso	21.0	Bayala et al. (2014)
	Cantinoa carpinifolia	DL	Brazil	7.5[a]	de Sá et al. (2016)
	Cantinoa heterodon	FAP	Brazil	7.90	Bridi et al. (2020)
	Cantinoa mutabilis	FAP	Brazil	12.2	Bridi et al. (2020)
	Cantinoa mutabilis	FAP	Brazil	12.4[a]	Silva et al. (2013b)
	Cantinoa stricta	FAP	Brazil	24.1	Bridi et al. (2020)
	Cantinoa sylvularum	FAP	Brazil	6.40	Bridi et al. (2020)
	Eplingiella fruticosa	FL	Brazil	6.2	Franco et al. (2011b)
	Eplingiella fruticosa	FF	Brazil	6.4	Franco et al. (2011b)
	Eplingiella fruticosa	FL	Brazil	7.3[a]	Franco et al. (2011a)
	Eplingiella fruticosa	DL	Brazil	14.8	Beserra-Filho et al. (2019)
	Hypenia salzmanii	FL	Brazil	14.4	Oliveira de Souza et al. (2017)
	Hyptidendron canum	FL	Brazil	22.5[a]	Fiuza et al. (2010)
	Hyptidendron canum	FF	Brazil	17.5[a]	Fiuza et al. (2010)
	Hyptis atrorubens	DAP	Martinique	18.3[a]	Kerdudo et al. (2016)
	Hyptis brevipes	DAP	China	9.7	Xu et al. (2013)
	Hyptis crenata	DL	Brazil	8.0[a]	Zoghbi et al. (2002)
	Hyptis dilatata	FL	Brazil	5.7	Almeida et al. (2018)
	Hyptis lanceolata	FL	Cameroon	6.8	Tchoumbougnang et al. (2005)
	Hyptis monticola	FAP	Brazil	11.3	Perera et al. (2017)
	Marsypianthes burchellii	DAP	Brazil	5.0[a]	Hashimoto et al. (2014)
	Marsypianthes chamedrys	FAP	Brazil	12.2	Callejon et al. (2016)
	Marsypianthes chamedrys	DAP	Brazil	11.5[a]	Hashimoto et al. (2014)
	Marsypianthes foliolosa	DAP	Brazil	7.0[a]	Hashimoto et al. (2014)
	Marsypianthes montana	DAP	Brazil	8.44[a]	Hashimoto et al. (2014)
	Medusantha martiusii	FL	Brazil	6.2	Costa et al. (2005)
	Medusantha martiusii	FAP	Brazil	6.1	Araújo et al. (2003)
	Mesosphaerum pectinatum	FL	Cameroon	22	Tchoumbougnang et al. (2005)
	Mesosphaerum pectinatum	DL	Brazil	28.3	Nascimento et al. (2008)
	Mesosphaerum pectinatum	DL	Brazil	24.3[a]	Arrigoni-Blank et al. (2008)
	Mesosphaerum pectinatum	FL	Brazil	30.9	Oliveira de Souza et al. (2017)
	Mesosphaerum pectinatum	DL	Brazil	25.6[a]	Feitosa-Alcantara et al. (2017)
	Mesosphaerum suaveolens	DAP	Brazil	10.4	Luz et al. (1984)
	Mesosphaerum suaveolens	FL	Australia	29.0	Peerzada (1997)
	Mesosphaerum suaveolens	DAP	Brazil	10.4[a]	Azevedo et al. (2002)
	Mesosphaerum suaveolens	FL	Cameroon	9.5	Tchoumbougnang et al. (2005)
	Mesosphaerum suaveolens	FL	Nigeria	5.5[a]	Eshilokun et al. (2005)
	Mesosphaerum suaveolens	DAP	China	16.2	Xu et al. (2013)
	Mesosphaerum suaveolens	FL	India	9.5	Sharma et al. (2019)
	Oocephalus oppositiflorus	FL	Brazil	14.3	Silva et al. (2000)
	Oocephalus oppositiflorus	FS	Brazil	8.6	Silva et al. (2000)
	Rhaphiodon echinus	DL	Brazil	23.1	Duarte et al. (2016)
***β*-elemene (263)**	*Cantinoa althaeifolia*	FAP	Brazil	6.60	Bridi et al. (2020)
	Cantinoa sylvularum	FAP	Brazil	7.60	Bridi et al. (2020)
	Hyptis lanceolata	FL	Cameroon	6.8	Tchoumbougnang et al. (2005)

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Table 2 (*continued*)

Compound	Species	Plant parts	Origin	Amount (%)	Reference
	Mesosphaerum pectinatum	FL	Cameroon	5.8	Tchoumbougnang et al. (2005)
	Mesosphaerum pectinatum	DL	Brazil	8.2[a]	Feitosa-Alcantara et al. (2018)
Bicyclogermacrene (264)	*Cantinoa mutabilis*	FAP	Brazil	9.3[a]	Silva et al. (2013b)
	Cantinoa mutabilis	FAP	Brazil	9.50	Bridi et al. (2020)
	Cantinoa stricta	FAP	Brazil	22.3	Bridi et al. (2020)
	Eplingiella fruticosa	FL	Brazil	7.3	Franco et al. (2011b)
	Eplingiella fruticosa	FL	Brazil	7.5[a]	Franco et al. (2011a)
	Eplingiella fruticosa	DL	Brazil	14.1	Beserra-Filho et al. (2019)
	Hyptidendron canum	FL	Brazil	22.6[a]	Fiuza et al. (2010)
	Hyptidendron canum	FF	Brazil	14.1[a]	Fiuza et al. (2010)
	Hyptis villosa	DL	Brazil	6.2	Silva et al. (2013a)
	Marsypianthes chamedrys	FAP	Brazil	17.9	Callejon et al. (2016)
	Marsypianthes chamedrys	DAP	Brazil	12.0[a]	Hashimoto et al. (2014)
	Marsypianthes foliolosa	DAP	Brazil	9.53[a]	Hashimoto et al. (2014)
	Marsypianthes montana	DAP	Brazil	41.4[a]	Hashimoto et al. (2014)
	Medusantha martiusii	FL	Brazil	6.3	Costa et al. (2005)
	Medusantha martiusii	FAP	Brazil	6.3	Araújo et al. (2003)
	Mesosphaerum suaveolens	DAP	Brazil	7.4[a]	Azevedo et al. (2002)
	Mesosphaerum suaveolens	FAP	Venezuela	15.7	Tesch et al. (2015)
	Rhaphiodon echinus	DL	Brazil	28.1	Duarte et al. (2016)
***cis*-calamenene (265)**	*Oocephalus oppositiflorus*	FS	Brazil	11.4	Silva et al. (2000)
***epi*-zonarene (266)**	*Oocephalus oppositiflorus*	FL	Brazil	7.0	Silva et al. (2000)
	Oocephalus oppositiflorus	FS	Brazil	7.9	Silva et al. (2000)
γ-cadinene (267)	*Condea emoryi*	DL	USA	6.7	Tanowitz et al. (1984)
	Oocephalus oppositiflorus	FL	Brazil	14.7	Silva et al. (2000)
	Oocephalus oppositiflorus	FS	Brazil	13.8	Silva et al. (2000)
	Oocephalus oppositiflorus	FF	Brazil	14.4	Silva et al. (2000)
δ-elemene (268)	*Mesosphaerum suaveolens*	DAP	Brazil	13.6	Luz et al. (1984)
Germacrene D (269)	*Cantinoa heterodon*	FAP	Brazil	16.3	Bridi et al. (2020)
	Cantinoa mutabilis	FAP	Brazil	10.2[a]	Silva et al. (2013b)
	Cantinoa stricta	FAP	Brazil	10.8	Bridi et al. (2020)
	Hyptis lanceolata	FL	Cameroon	19.9	Tchoumbougnang et al. (2005)
	Hyptis monticola	FAP	Brazil	6.9	Perera et al. (2017)
	Marsypianthes burchellii	DAP	Brazil	12.4[a]	Hashimoto et al. (2014)
	Marsypianthes chamedrys	FAP	Brazil	34.1	Callejon et al. (2016)
	Marsypianthes chamedrys	DAP	Brazil	25.5[a]	Hashimoto et al. (2014)
	Marsypianthes foliolosa	DAP	Brazil	12.4[a]	Hashimoto et al. (2014)
	Marsypianthes montana	DAP	Brazil	25.0[a]	Hashimoto et al. (2014)
	Mesosphaerum pectinatum	FL	Cameroon	28.0	Tchoumbougnang et al. (2005)
	Mesosphaerum suaveolens	DAP	Brazil	5.5[a]	Oliveira et al. (2005)
	Mesosphaerum suaveolens	FAP	Venezuela	8.2	Tesch et al. (2015)
Isocaryophyllene (270)	*Hyptis rhomboidea*	DAP	China	7.5	Xu et al. (2013)
	Mesosphaerum suaveolens	DAP	China	9.9	Xu et al. (2013)
***trans*-α-bergamotene (271)**	*Mesosphaerum suaveolens*	FL	Cameroon	10.9	Tchoumbougnang et al. (2005)
***trans*-Cadina-1(6),4-diene (272)**	*Cantinoa carpinifolia*	DL	Brazil	6.2[a]	de Sá et al. (2016)
Amorpha-4,7(11)-diene (273)	*Hyptidendron canum*	FL	Brazil	22.6[a]	Fiuza et al. (2010)
Germacrene A (274)	*Cantinoa althaeifolia*	FAP	Brazil	7.50	Bridi et al. (2020)
	Cantinoa heterodon	FAP	Brazil	13.9	Bridi et al. (2020)
	Cantinoa sylvularum	FAP	Brazil	6.30	Bridi et al. (2020)
β-selinene (275)	*Cantinoa althaeifolia*	FAP	Brazil	5.60	Bridi et al. (2020)
7-*epi*-α-selinene (276)	*Cantinoa althaeifolia*	FAP	Brazil	21.6	Bridi et al. (2020)
γ-gurjunene (277)	*Cantinoa sylvularum*	FAP	Brazil	6.80	Bridi et al. (2020)
γ-himachalene (278)	*Cantinoa althaeifolia*	FAP	Brazil	12.2	Bridi et al. (2020)
α-cadinol (279)	*Eplingiella fruticosa*	S	Brazil	8.6	Franco et al. (2011a)
	Hyptis villosa	DL	Brazil	5.2	Silva et al. (2013a)
α-muurolol (280)	*Hyptis monticola*	FAP	Brazil	6.4	Perera et al. (2017)
Aromadendr-1(10)-en-9-one (281)	*Condea verticillata*	FAP	Jamaica	15.1	Facey et al. (2005)
Cadina-4,10(15)-dien-3-one (282)	*Condea verticillata*	FAP	Jamaica	30.7	Facey et al. (2005)
Calamusenone (283)	*Mesosphaerum pectinatum*	DL	Brazil	18.9[a]	Arrigoni-Blank et al. (2008)
Caryophyllene oxide (284)	*Cantinoa mutabilis*	FAP	Brazil	24.8	Bridi et al. (2020)
	Hypenia salzmanii	FL	Brazil	5.4	Oliveira de Souza et al. (2017)
	Hyptis atrorubens	DAP	Martinique	19.6	Kerdudo et al. (2016)
	Marsypianthes burchellii	DAP	Brazil	5.0[a]	Hashimoto et al. (2014)
	Marsypianthes chamedrys	DAP	Brazil	7.0[a]	Hashimoto et al. (2014)
	Marsypianthes foliolosa	DAP	Brazil	10.3[a]	Hashimoto et al. (2014)
	Mesosphaerum pectinatum	DL	Brazil	28.0	Nascimento et al. (2008)
	Mesosphaerum pectinatum	FL	Brazil	13.2	Oliveira de Souza et al. (2017)
	Mesosphaerum pectinatum	DL	Brazil	16.9[a]	Feitosa-Alcantara et al. (2018)
	Mesosphaerum suaveolens	DAP	Brazil	6.9[a]	Azevedo et al. (2002)
	Rhaphiodon echinus	DL	Brazil	5.4	Duarte et al. (2016)
Elemol (285)	*Condea emoryi*	DL	USA	7.0	Tanowitz et al. (1984)
***epi*-α-cadinol (286)**	*Hyptis villosa*	DL	Brazil	8.9	Silva et al. (2013a)
Globulol (287)	*Cantinoa heterodon*	FAP	Brazil	10.7	Bridi et al. (2020)
	Cantinoa mutabilis	DL	Brazil	11.9	Aguiar et al. (2003)
	Cantinoa mutabilis	FAP	Brazil	20.8[a]	Silva et al. (2013b)
	Cantinoa mutabilis	FAP	Brazil	46.2	Bridi et al. (2020)

(*continued on next page*)

Table 2 (*continued*)

Compound	Species	Plant parts	Origin	Amount (%)	Reference
	Cantinoa sylvularum	FAP	Brazil	40.8	Bridi et al. (2020)
	Marsypianthes burchellii	DAP	Brazil	10.1[a]	Hashimoto et al. (2014)
	Oocephalus oppositiflorus	FL	Brazil	6.9	Silva et al. (2000)
	Oocephalus oppositiflorus	FS	Brazil	7.2	Silva et al. (2000)
	Oocephalus oppositiflorus	FF	Brazil	16.8	Silva et al. (2000)
Guaiol (288)	*Oocephalus oppositiflorus*	FL	Brazil	10.7	Silva et al. (2000)
	Oocephalus oppositiflorus	FF	Brazil	9.4	Silva et al. (2000)
Kessane (289)	*Hyptis villosa*	DL	Brazil	9.1	Silva et al. (2013a)
Prenopsan-8-ol (290)	*Cantinoa carpinifolia*	DL	Brazil	7.2[a]	de Sá et al. (2016)
Spathulenol (291)	*Eplingiella fruticosa*	S	Brazil	22.6	Franco et al. (2011a)
	Hyptis villosa	DL	Brazil	17.3	Silva et al. (2013a)
	Marsypianthes burchellii	DAP	Brazil	21.3[a]	Hashimoto et al. (2014)
	Marsypianthes chamedrys	DAP	Brazil	13.4[a]	Hashimoto et al. (2014)
	Marsypianthes foliolosa	DAP	Brazil	26.4[a]	Hashimoto et al. (2014)
	Mesosphaerum pectinatum	FL	Brazil	5.7	Oliveira de Souza et al. (2017)
	Mesosphaerum suaveolens	DAP	Brazil	15.4[a]	Azevedo et al. (2002)
	Rhaphiodon echinus	DL	Brazil	5.1	Duarte et al. (2016)
Cubebol (292)	*Mesosphaerum sidifolium*	FL	Brazil	24.8	Rolim et al. (2017)
τ - muurolol (293)	*Cantinoa sylvularum*	FAP	Brazil	8.60	Bridi et al. (2020)
Selin 11-em-4-α-ol (294)	*Cantinoa althaeifolia*	FAP	Brazil	7.80	Bridi et al. (2020)
14-hydroxy- α –humulene (295)	*Cantinoa althaeifolia*	FAP	Brazil	7.50	Bridi et al. (2020)

[a] Averaged amount from different collections of the same species. S = seeds; DL = dried leaves; DF = dried flowers; FL = fresh leaves; FF = fresh flowers; FS = fresh stems; DAP = dried aerial parts; FAP = fresh aerial parts.

essential oils, which are frequent in several members of the family. Some species of Hyptidinae are also popularly used as insecticides and pest repellents, probably because they are markedly aromatic. In some cases, the effects have been demonstrated by scientific investigations, as shown below.

In 1995, Porter et al. (1995). described the activity of cadina-4,10(15)-dien-3-one (**282**), isolated from *Condea verticillata* (syn. *Hyptis verticillata*), against the cattle tick, *Boophilus microplus* (avoiding the oviposition, but being ineffective in adult ticks), and toxic action against adult *Cylas formicarius elegantulus* (3.6 mg/g), a destructive pest of sweet potato (*Ipomoea* sp.). Another study demonstrated insecticidal activity of the essential oil from the same species against the insect cited above. This oil presented as main compounds, the oxygenated sesquiterpenoids aromadendr-1(10)-en-9-one (**281**) (ca. 31%) and cadina-4,10(15)-dien-3-one (**282**) (ca. 15%) (Facey et al., 2005).

Some labdane diterpenes isolated from *Cantinoa americana* (syn. *Hyptis spicigera*) were tested in a bioassay on larval toxicity of the European corn borer, *Ostrinia nubilalis*. The compound 15,19-diacetoxy-2*R*,7*R*-dihydroxylabda-8(17),(13Z)-diene (**67**) significantly inhibited the larval growth (Fragoso-Serrano et al., 1999). From the same species, an essential oil composed mainly by *α*-pinene (**238**), *β*-phellandrene (**240**), *β*-pinene (**241**), sabinene (**246**) and 1,8-cineole (**250**), exhibited activity against the cowpea weevil (*Callosobruchus maculatus*), the major cause of damages in cowpea (*Vigna unguiculata*) (Noudjou et al., 2007). These studies validated the popular use of the leaves of this species as insect repellent by an indigenous group from Ghana (Asase et al., 2005). In addition, the powder obtained from the dry plants of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) also demonstrated activity against the cowpea weevil (Melo et al., 2015).

In the context of agricultural losses, more than 100 insect species are known to live and feed on stored peanuts, some of them with economic importance, being the cadelle (*Tenebroides mauritanicus*), one of the most commonly reported pests (Coskuncu and Kovanci, 2005). Searching for insecticidal agents, the essential oil from the fresh leaves of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), constituted mainly by 1,8-cineole (**250**) and *β*-caryophyllene (**262**), was tested against this pest. The results revealed that a concentration of 0.5 μL of essential oil/g of peanut is enough to cause 100% of mortality after 24 h, indicating the potential of this oil in the protection against *Tenebroides mauritanicus* and reduction of post-harvest losses (Adjou et al., 2019).

The essential oil extracted from the fresh leaves of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), presenting terpinolene (**247**) as the main compound, demonstrated insecticidal activity against *Aedes albopictus* larvae (400–450 ppm), and similarly showed a good repellent action (RD_{50} 0.00035 μg/cm^2; RD_{90} 0.00048 μg/cm^2) (Conti et al., 2011). Other study carried out with the essential oil of the above-cited species, composed mainly by *α*-phellandrene (**237**), sabinene (**246**) and 1,8-cineole (**250**), demonstrated repellent properties against nymphs of the tick *Ixodes ricinus* (Ashitani et al., 2015). These studies corroborate reports of ethnobotanical uses of this species against pests (Seyoum et al., 2002), including those that are vectors of diseases such as malaria (Attah et al., 2012), among others (Sonibare et al., 2015).

Bioinseticides are promising eco-friendly substitutes to the chemical insecticides. This approach is interesting because these agents can be more selective and may last for shorter periods in the environment (Soberón et al., 2016). In this context, Elumalai et al. (2017) described the synthesis of silver nanoparticles produced with the aqueous extracts from the leaves of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) and its insecticidal activity. The results demonstrated 100% of mortality (10 μg/mL) of *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus*, the vectors of malaria, dengue and filariasis, respectively. These findings suggest that the nanoparticles have potential to be used as an ideal eco-friendly agent for the control of the mosquito larvae. Other study reported the activity of a petroleum ether extract of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) against *Culex quinquefasciatus* (LC_{50} 38.39 μg/mL) and *Aedes aegypti* (LC_{50} 64.49 μg/mL) (Hari and Mathew, 2018).

The essential oil from another species of the genus, *Medusantha martiusii* (syn. *Hyptis martiusii*) and its main component, 1,8-cineole (**250**), were tested against *Aedes aegypti* larvae showing an effect at the concentrations of 250 and 100 mg/mL, respectively (Araújo et al., 2003). This activity was further confirmed by other authors that demonstrated a CL_{50} of 18.2 ppm of the essential oil against *Aedes aegypti* in addition to 27.5 ppm to *Culex quinquefasciatus* (Costa et al., 2005).

Among the pests that affect agriculture in the Neotropical region, leaf cutting ants such as *Acromyrmex balzani* Emery (Hymenoptera: Formicidae), cause damages that can reach billions of dollars per year (Montoya-Lerma et al., 2012). Thus, the essential oils of *Eplingiella fruticosa*, from four genotypes with different levels of monoterpenes, were investigated concerning its toxicity on *Acromyrmex balzani* populations. The results demonstrated LC_{50} values from 4.54 to 6.78 μL/L, being the genotypes with higher contents of monoterpenes the most active. In order to reinforce the data obtained with the essential oils, the isolated

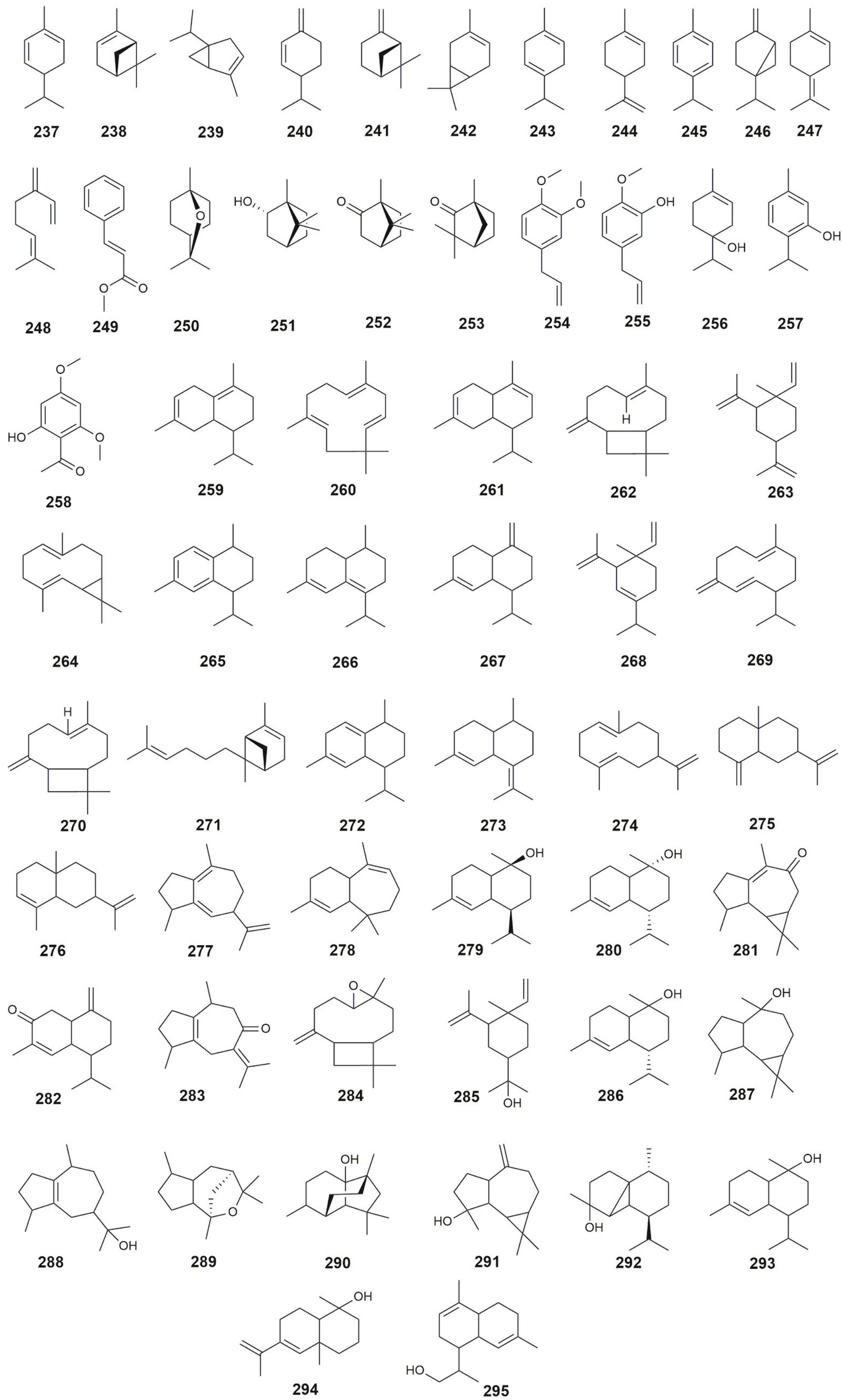

Fig. 7. Composition of essential oils (**183**–**229**) from Hyptidinae species.

compounds 1,8-cineol (**250**), camphor (**252**), β-caryophyllene (**262**) and caryophyllene oxide (**284**) were also tested. The data corroborate the former results, indicating that the activity was principally provided by the monoterpenes 1,8-cineol (**250**) and camphor (**252**), whose LC_{50} values were 1.05 μL/L and 2.46 μL/L, respectively (Silva et al., 2019).

As it can be seen, most of the above-mentioned studies, with rare exceptions, refer to essential oils, and reinforce data found in the literature that point these compounds as the next generation of pesticides.

5.2. Antimicrobial activity

There are reports in literature demonstrating the effects of extracts and/or isolated compounds of Hyptidinae species against infectious diseases-causing agents. In order to provide a better understanding of the data acquired from literature, this section was divided into antibacterial, antifungal, antiviral and antiprotozoal activities.

5.2.1. Antibacterial activity

Bacteria are microorganisms that are part of normal intestinal flora, where they help digest the food, for example. However, determined species can invade the body, causing serious diseases. There are specific drugs to treat these infections but their inappropriate use led to development of resistant microorganisms (Lesho and Laguio-Vila, 2019). Nowadays, antibiotic resistance is one of the biggest public health challenges, making new treatment alternatives imperative to overcome this issue. In this sense, there are several studies in literature showing the antibacterial efficacy of essential oils, extracts and isolated compounds obtained from different species of Hyptidinae. These reports demonstrate the potential of these species as a source of products endowed with this action.

The essential oil of *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) demonstrated a slightly inhibitory effect (MIC 200 μg/mL) against clinical isolated (patients saliva) and ATCC strains (10 449 and 25 175) of *Streptococcus mutans* (Nascimento et al., 2008). The same species afforded the α-pyrone pectinolide H (**157**), which was active against multidrug resistant strains of *Staphylococcus aureus* (MIC 32–64 μg/mL) (Fragoso-Serrano et al., 2005). These results could justify the use of the referred species as antiseptic by Mexican populations, for example (Rojas et al., 1992). In another study with this species, Tesch et al. (2015) compared the antibacterial activity of essential oils from the leaves and flowers and found a weak activity against gram negative bacteria strains from Enterobacteriaceae family: *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella typhi* with MIC values between 300 and 450 μg/mL.

Violante et al. (2012) reported the antibacterial activity of an ethyl acetate fraction of *Hyptis crenata* against *Enterococcus faecalis* (MIC 31.3 μg/mL) and a dichloromethane fraction against *Staphylococcus aureus* (MIC 62.5 μg/mL) and *Enterococcus faecalis* (MIC 62.5 μg/mL). On the other hand, the ethanolic extract of *Mesosphaerum sidifolium* (syn. *Hyptis sidifolia* (L'Hér.) Briq.) was investigated against *Staphylococcus aureus* showing low antibacterial activity (MIC 1000 μg/mL) (Bussmann et al., 2010).

The essential oils from *Hyptis brevipes*, presenting methyl eugenol (**254**), 3-allylguaiacol (**255**) and β-caryophyllene (**262**) as the main compounds, and from *Hyptis rhomboidea*, whose main compounds were isocaryophyllene (**270**) and β-cadinene (**261**), have demonstrated to be effective against strains of *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa* (MICs 3.125–50 μg/mL), being *Hyptis brevipes* oil slightly more effective (Xu et al., 2013).

The influence of seasonality on the chemical composition of the essential oil from leaves of *Hyptis dilatata* was assessed by Almeida et al. (2018). The samples were tested against gram positive (*Staphylococcus aureus* and *Bacillus cereus*) and gram negative bacteria (*Salmonella typhimurium* and *Citrobacter freundii*). The authors reported that the essential oil from leaves collected in dry period, had more potential to inhibit the growth of *Bacillus cereus* (IC_{50} = 112.8 μg/mL and leaves collected in the rainy season, generated an oil more effective against *Staphylococcus aureus* (IC_{50} = 78.8 μg/mL). Nevertheless, there was no difference in the components of the essential oils, only quantitatively, explaining the slightly differences in activities. The samples presented better results on gram positive bacteria strains, which could be explained by their simpler structures in comparison to the gram negative ones.

The methoxylated flavones cirsilineol (**202**) and cirsimaritin (**203**), obtained from *Condea undulata* (syn. *Hyptis fasciculata*) possess a potent activity against *Helicobacter pylori* exhibiting IC_{90} of 3.2 and 6.3 μg/mL, respectively (Isobe et al., 2006). This result could encourage researchers in evaluate the potential of this species as a source of agents to treat gastrointestinal diseases since the presence of this microorganism increases the relative risk of developing some clinical disorders in the upper gastrointestinal tract (Kusters et al., 2006).

Interestingly, Costa et al. (2017) evaluated the capacity of aqueous and ethanolic extracts from *Rhaphiodon echinus* (Nees & Mart.) Schauer. to enhance the effects of some antimicrobials against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The results demonstrated that both extracts were able to improve the MIC of gentamicin and amikacin in *Escherichia coli* strains. On the other hand, only the aqueous extract was effective in increasing the activity of imipenem and gentamicin against *Pseudomonas aeruginosa*. No effects were observed on *Staphylococcus aureus*. In addition, the essential oil of the same plant also was capable of modulate the activity of antibacterial drugs such as gentamicin, amikacin, imipenem and ciprofloxacin. In fact, the presence of the oil increased the MIC of the amikacin against *Escherichia coli*, suggesting an antagonic effect. On the other hand, it seems to have a synergic effect of the oil with gentamicin, amikacin and ciprofloxacin in *Pseudomonas aeruginosa* strains (Duarte et al., 2016).

Recently, Sedano-Partida et al. (2020) evaluated the antibacterial potential of *Hyptis radicans* (syn. *Peltodon radicans*) and *Hyptis multibracteata* Benth. The results demonstrated that hexane and ethyl acetate extracts from *Hyptis multibracteata* presented potent antibacterial activity against *Bacilus subtilis* (MICs 23.6 and 12.13 μg/mL, respectively). In addition, the hexane extract of the above-mentioned species was also effective against *Pseudomonas aeuruginosa* (MIC 37.55 μg/mL).

5.2.2. Antifungal activity

Fungal infections are associated with high morbidity and mortality rates. These infections are a global public health problem, mainly in immunocompromised patients. The treatment options are limited due to a few number of therapeutic classes available (Hadrich and Ayadi, 2018) in addition to the increase of resistance cases. Therefore, new therapeutic options are highly needed.

In this sense, the essential oils from *Hyptis brevipes* and *Hyptis rhomboidea*, that also exhibited antibacterial activity, were investigated showing activity against strains of *Fusarium graminearum*, *Botrytis cinerea*, *Exerohilum turcicum* and *Lecannosticta acicola* (MICs 3.125–50 μg/mL), being *Hyptis brevipes* essential oil slightly more effective (Xu et al., 2013).

The antifungal activity of an ethanolic extract of *Hyptis crenata* was investigated against several leveduriform fungal species. The most promising activities were found against *Candida krusei* and *Cryptococcus neoformans* species (MIC 125 μg/mL) (Violante et al., 2012). Additionally, hexanic (96.9% inhibition) and chlorophormic (96.9% inhibition) fractions from the leaves of *Hyptidendron canum* (syn. *Hyptis cana*), as well as ursolic acid (**78**) (90.9% inhibition) showed antifungal activities against the yeast form of *Paracoccidioides brasiliensis* (Lemes et al., 2011). On the other hand, *Medusantha martiusii* (syn. *Hyptis martiusii*) ethanolic extract was tested against this some *Candida* strains and did not exhibit antifungal activity (MIC $\geq$ 1024 μg/mL) (Santos et al., 2013).

Still addressing leveduriform fungal species, Costa et al. (2017) demonstrated that the association of the aqueous or ethanolic extracts of *Rhaphiodon echinus* with the antifungal drug nystatin causes an antagonic effect in the drug activity against *Candida albicans* and *Candida* *tropicalis*. Indeed, this combination (using aqueous extract) provoked a reduction in the MIC of nystatin against *Candida krusei*. Besides, the essential oil of the same species was also capable to modulate the activity of fluconazole reducing the MIC value of the drug against *Candida krusei* and *Candida tropicalis* (Duarte et al., 2016).

Mesosphaerum suaveolens (syn. *Hyptis suaveolens*) is used in popular medicine to treat fungal infections by applying a paste made from the crushed leaves on the affected area (Wiart et al., 2004; Policepatel and Manikrao, 2013). Thus, aqueous extracts from the leaves and aerial parts of this plant were assessed in association with fluconazole, an antifungal drug commercially available. The results showed that the extract from the leaves modulated the fluconazole activity against *Candida albicans*. Furthermore, the extract from the aerial parts also demonstrated potentiating effects of the drug, both to *Candida albicans* and *Candida parapsilosis* strains (Costa et al., 2020).

5.2.3. Antiviral activity

A virus is a small infectious organism that must invade a living cell to reproduce. Some viruses, such as hepatitis B and hepatitis C, can cause chronic infections that could last for years (Kramer et al., 2008). In the last decade, the influenza virus (A:H1N1pdm09) has drawn attention by the pandemic that provoked morbidity and mortality (WHO, 2010). More recently, the outbreak of the novel coronavirus (SARS-CoV-2), that has affected more than 9 million patients all over the world, has become a major global health concern (WHO, 2020), and efforts must be done in order to prevent the virus spread.

There are few reports about the antiviral activity of Hyptidinae extracts, essential oils or isolated compounds. The anti-HIV activity of oleanolic acid (**75**) (IC_{50} 21.8 μg/mL) and pomolic acid (**88**) (IC_{50} 23.3 μg/mL), isolated from *H. capitata*, was demonstrated (Kashiwada et al., 1998). Almost 20 years later, a report showed the activity of the essential oil from *Cantinoa mutabilis* (syn. *Hyptis mutabilis*), containing 1, 8-cineole (**250**), fenchone (**253**), bicyclogermacrene (**264**) and *β*-caryophyllene (**262**) as the main compounds, on human herpes viruses types 1 and 2, respectively, at a concentration of 50 μg/mL (Brand et al., 2016).

The species from Hyptidinae are widely used in the popular medicine to treat respiratory diseases (see Table 1) which could be caused by virus. Despite that, investigations in this sense were not carried out. Scientific studies evaluating the antiviral activity of extracts or compounds obtained from these plants would be pertinent in light of the growing prevalence of viral infections.

5.2.4. Antiprotozoal activity

Protozoa are microscopic, one-celled organisms that can be free-living or parasitic in nature. They are able to multiply in humans, which contributes to their survival and also allows serious infections to develop from just a single organism (CDC, 2019). Therefore, the combat of these parasites is a matter of major importance.

According to the WHO (2018), only in 2017, approximately 435 000 malaria deaths occurred worldwide due to *Plasmodium falciparum* infections. Therefore, studies aiming at finding antimalarial agents are highly relevant. In this context, some species of Hyptidinae were investigated. The results showed that the ethanolic extract from *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) displayed high antiplasmodial activity against a chloroquine-sensitive strain of *Plasmodium falciparum* (IC_{50} 3.9 μg/mL)(Noronha et al., 2018). Furthermore, the abietane diterpene, 13-*epi*-dioxiabiet-8(14)-en-18-ol (**6**), isolated from the same species, exhibited antiplasmodial activity (IC_{50} 100 μg/mL) (Chukwujekwu et al., 2005).

Other parasite with high mortality rates is *Leishmania* that is endemic in more than 98 countries on five continents (WHO, 2019a). Thus, efforts must be pursued in order to diminish the incidence of this parasite. In this backdrop, as species of Hyptidinae are used as leishmanicidal agents, some of them were investigated demonstrating promising results. An ethanolic extract of *Hyptis lacustris* A.St.-Hill ex Benth revealed interesting activity (IC_{50} < 10 μg/mL) against amastigote forms of *L. amazonensis* (Céline et al., 2009), corroborating the use of this species in folk medicine to treat leishmaniasis (Céline et al., 2009). Still addressing the anti-*Leishmania* effect, *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) extracts (hexanic, ethyl acetate, ethanolic and hydromethanolic), and the isolated compounds 3-*O*-methyl-rosmarinic acid (**223**), sambacaitaric acid (**225**) and 3-*O*-methyl-sambacaitaric acid (**226**) exhibited leishmanicidal activity against the promastigote forms of *L. braziliensis* (Falcão et al., 2013). Other authors have reported the anti-*Leishmania* activity of an aqueous extract of the last cited species in the *L. amazonensis* promastigotes (100 μg/mL) and amastigotes (10 μg/mL) (de Queiroz et al., 2014).

Chagas disease is another serious public health problem. An estimated 8 million people are infected with *Trypanosoma cruzi* worldwide, mainly in Latin America, causing more than 10 000 deaths per year. Nowadays, chemotherapy is the only available treatment for this disease, and the drugs currently used present high toxicity levels (WHO, 2019b). Therefore, the discovery of new drugs is very important. In this sense, the essential oils of *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) and *Hypenia salzmannii* demonstrated to be effective against all *Trypanosoma cruzi* forms, epimastigote (IC_{50} = 56.1 μg/mL; 42.13 μg/mL), trypomastigote (IC_{50} = 25.6 μg/mL; 36.27 μg/mL) and amastigote (IC_{50} = 25.5 μg/mL; 35.25 μg/mL). Besides, the selectivity index for amastigotes and epimastigotes were suitable to the development of promising products with trypanocidal activity (Oliveira de Souza et al., 2017b).

The activity of a species from Hyptidinae against the protozoan parasite *Ichthyophthirius multifiliis* has also been reported. This protozoa affects the economically important fish *Rhamdia quelen (*silver catfish), the most raised native species in South America (Gomes et al., 2000). Therefore, the essential oil from the leaves of *Cantinoa mutabilis* (syn. *Hyptis mutabilis*), as well as its major component, globulol (**287**) were tested against this parasite. The results of this research evidenced that both, essential oil and the isolated compound increased the survival of the infected fish (da Cunha et al., 2017).

Finally, an extract from the aerial parts of *Condea albida* (syn. *Hyptis albida*) obtained with a mixture of dichloromethane and methanol (1:1) demonstrated effectiveness against strains of *Trichomonas vaginalis* (GT-13) (MIC 11.4 μg/mL) and *Giardia lamblia* (0989:IMSS) (MIC 16.1 μg/mL) (Camacho-Corona et al., 2015). The effect against *Giardia lamblia* could explain the use of this plant for the treatment of gastrointestinal disturbances (Martínez, 1979).

5.3. Antinociceptive activity

The first study with this purpose was carried out with *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) using the writhing test. The oral administration of leaves extracts (hexane, chloroform and ethyl acetate) (100, 200, 400 mg/kg of body weight in mice) significantly reduced the number of writhing induced by acetic acid and increased the response to thermal stimuli in hot-plate test (Lisboa et al., 2006). In the same year, oleanoic acid (**68**), isolated from *Eriope blanchetii*, showed capability to inhibit capsaicin evoked acute nociception due to mechanisms possibly involving opioid receptors, nitric oxide, and K^+ ATP channels (Maia et al., 2006).

Subsequently, the antinociceptive activity of the essential oils obtained from of six genotypes of *Mesosphaerum pectinatum* (syn. *Hyptis pectinata*) (100, 200, 400 mg/kg of body weight in mice), was investigated using abdominal writhing induced by acetic acid and hot plate tests. The results demonstrated that the essential oils from all genotypes have antinociceptive effect, in both models used. These results are relevant facing the demonstration of peripheral (writhes reduction) and central antinociceptive effects (hot plate) (Arrigoni-Blank et al., 2008).

More recently, Falcão et al. (2016) described the antinociceptive action of an ethyl acetate fraction from the leaves of the above-cited species and its main constituent, rosmarinic acid (**222**) (formalin, glutamate and capsaicin induced orofacial nociception in rodents). The results evidenced that the oral administration of the extract produced potent antinociceptive effects when compared with its main constituent. In spite of rosmarinic acid (**222**) be the main component of the tested fraction, the presented action is probably due to an additive or synergism effect among the metabolites extracted with ethyl acetate. Together, these findings (Lisboa et al., 2006; Arrigoni-Blank et al., 2008; Falcão et al., 2016) support the use of this species in the Brazilian folk medicine to treat headaches, toothaches and liver neuropathic pain (de Albuquerque et al., 2007).

Still addressing antinociceptive action, the essential oil of *Eplingiella fruticosa* (syn. *Hyptis fruticosa*) exhibited antinociceptive activity (acetic acid-induced writhing) at doses of 100, 200, and 400 mg/kg (s.c.) (Menezes et al., 2007). Other authors corroborated these results, testing three samples of essential oils from leaves and flowers of the same species (acetic acid-induced writhing and formalin tests). All samples presented antinociceptive effect, being that with the high percentage of 1.8-cineole (**220**) (18.7%) the most effective (Franco et al., 2011b).

Chronic musculoskeletal pain disorders, such as fibromyalgia, affect approximately 20% of population and are associated with significant disability. The treatment of these conditions are extremely difficult and new alternatives aiming at improve the life quality of patients are needed. In this context, the essential oil of *Eplingiella fruticosa* (syn. *Hyptis fruticosa*) complexed with β-cyclodextrin was evaluated in a chronic widespread non-inflammatory muscle pain animal model (a mice fibromyalgia-like model). The results demonstrated an anti-hyperalgesic effect provoked by the essential oil, which was improved by the complexation with β-cyclodextrin (Melo et al., 2020), suggesting the use of this species in chronic pain management. Altogether, the studies with the above-cited species (Franco et al., 2011b; Melo et al., 2020; Menezes et al., 2007) support its popular use to relief pain.

The ethanolic extract from *Mesosphaerum sidifolium* (syn. *Hyptis umbrosa*) was assessed concerning its antinociceptive (acetic acid-induced writhing model, formalin, glutamate or capsaicin) and anti-inflammatory actions (peritonitis induced by the intrathoracic injection of carrageenan to quantify the total number of leukocytes) (100, 200 or 400 mg/kg of body weight in mice). The results demonstrated that the treatment with all doses produced a significant analgesia in the acetic acid-induced writhing model and in the glutamate and capsaicin tests. Furthermore, the extracts efficiently inhibited the carrageenan-induced leukocyte migration to the peritoneal cavity. Therefore, the authors suggest that the tested extracts hold peripheral analgesic action and showed potential in reducing the spreading of the inflammatory processes (dos Anjos et al., 2017).

There are some reports showing the use of *Cantinoa americana* (syn. *Hyptis spicigera*) in the folk medicine for pain relief (Tapsoba and Deschamps, 2006; Hajdu and Hohmann, 2012). Therefore, the effect of the essential oil from this species, constituted principally by the monoterpenes *α*-pinene (**238**), 1,8-cineole (**250**) and *β*-pinene (**241**), was evaluated using antinociceptive tests (formalin and transient receptor potential (TRP) channels agonists). The authors found that the essential oil presents antinociceptive effect at 300 and 1000 mg/kg on formalin-induced pain behavior model, presenting 50% and 72% of inhibition during the first phase ($ED_{50} = 292$ mg/kg), and 85% and 100% during de second phase ($ED_{50} = 205$ mg/kg), respectively. Temperature of the hind paw was also reduced by samples treatment in a dose-dependent manner (Simões et al., 2017).

5.4. Anti-ulcer activity

Gastric ulcer is one of the major gastrointestinal disorders, occurring due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors (Loren, 2016).

Aiming at finding new agents with ability of protecting the gastric mucosa, the effect of the essential oil obtained from the aerial parts of *Cantinoa americana* (syn. *Hyptis spicigera*), containing *α*-pinene (**238**), 1,8-cineole (**250**) and *β*-pinene (**241**), was evaluated for the gastroprotective and healing activities. The results of this study showed that the tested oil (100 mg/kg, p.o.) provided effective protection against lesions induced by absolute ethanol (97%) and nonsteroidal anti-inflammatory drug (NSAIDs) (84%) in rats. Furthermore, it seems that this effect is due to an increase in the gastric mucus production (28%) induced by prostaglandin-E_2 levels and a healing capacity (87%) could be observed (Takayama et al., 2011). In the same direction, Caldas et al. (2011) have demonstrated that the oral administration of *Medusantha martiusii* (syn. *Hyptis martiusii*) essential oil, principally composed by bicyclogermacrene (**264**) (100, 200, 40 mg/kg) inhibited the ethanol, HCl/ethanol and indomethacin-induced ulcers in rats. Ethnopharmacological data reinforce this result, since this species is used to treat intestinal and stomach diseases (Agra et al., 2008).

Standardized ethanolic extract containing 3.65 mg of kaempferol (**211**) by 100 g of dry plant and a hexane fraction from the leaves of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) were tested (62.5, 125, 250 and 500 mg/kg) in models of acute gastric ulcers. Both extracts were able to reduce the injuries caused by all ulcerogenic agents (HCl/ethanol, ethanol, NSAIDs and hypothermic restraint - stress) (Jesus et al., 2013). It is worth mentioning that there are reports of the popular use of this species in the treatment of ulcers (Ribeiro et al., 2017), gastrointestinal disorders (Jacobo-Herrera et al., 2016) and stomachache (Silambarasan and Ayyanar, 2015) which may be related to ulcerative problems.

5.5. Cytotoxic activity

The first study of cytotoxicity involving a species from Hyptidinae, published in 1979, reports the activity of the ethanolic extract from *Condea tomentosa* (syn. *Hyptis tomentosa*) in the KB cell culture system (ED_{50} 2.6 μg/mL) and the P-388 lymphocytic leukemia system (140–200 mg/kg). After a positive result exhibited by the extract, isolated compounds were tested against the KB cells, showing promising results: deoxypodophyllotoxin (**133**) (ED_{50} 0.032 μg/mL), 5-hydroxy-4′,6,7,8-tetramethoxyflavone (**192**) (ED_{50} 6.0 μg/mL) and 5-hydroxy-4′,3,6,7,8-pentamethoxyflavone (**193**) (ED_{50} 1.8 μg/mL) (Kingston et al., 1979).

In 1988, Yamagishi et al. described the isolation of two triterpene acids from *Hyptis capitata* with significant *in vitro* action in human colon tumor cells (HCT-8), hyptatic acid A (**90**) (ED_{50} 4.2 μg/mL) and 2*α*-hydroxyursolic acid (**86**) (ED_{50} 2.7 μg/mL). In the same way, lignans isolated from *Condea verticillata* (syn. *Hyptis verticillata*) were assayed for the cytotoxic activity on lymphocytic leukemia system (P-388). The compounds 4′-demethyldeoxypodophyllotoxin (**114**) (ED_{50} 0.005 μg/mL), 5-methoxydehydropodophyllotoxin (**116**) (ED_{50} 4 μg/mL), dehydro-*β*-peltatin-methyl ether (**117**) (ED_{50} 1.8 μg/mL), yatein (ED_{50} 0.4 μg/mL) (**120**), deoxypicropodophyllin (**122**) (ED_{50} 0.1 μg/mL), and *β*-apopicropodophyllin (**123**) (ED_{50} 0.002 μg/mL) demonstrated significant cytotoxic activity (Novelo et al., 1993). It is important to highlight that podophyllotoxin derivatives, such as etoposide, have been used for decades to treat various types of cancer (Stähelin and von Wartburg, 1991; Newman and Cragg, 2020).

Pectinolides A – C (**150**–**152**) exhibited *in vitro* cytotoxic activity on a panel of cancer cell lines with ED_{50} activities ranging from 0.1 to 3.3 μg/mL (Pereda-Miranda et al., 1993). More recently, the compounds **140** and **142**, demonstrated cytotoxic effects against KB cells (nasopharyngeal carcinoma) at concentrations of 0.63 and 2.52 μg/mL, respectively (Fragoso-Serrano et al., 2005). From *Medusantha martiusii* (syn. *Hyptis martiusii*), the abietane diterpenes carnosol (**14**), 11,14-dihydroxy-8,11,13-abietatrien-7-one (**39**), 7*β*-hydroxy-11,14-dioxoabieta-8,12-diene (**48**) and 7*α*-acetoxy-12-hydroxy-1,14-dioxoabieta-8,12-diene (**49**) were tested concerning their cytotoxic effect on leukemia (HL-60 and CEM), breast (MCF-7), colon (HCT-8) and skin (B-16) cancer cell lines. These compounds exhibited cytotoxic activity against this panel of cell lines with IC_{50} values ranging from 1.9 to 67 μM (Araújo et al., 2006;

Costa-Lotufo et al., 2004). Furthermore, Fronza et al. (2011) evidenced high cytotoxic effect of 7α-acetoxyroyleanone (**25**), an abietane diterpene isolated from the roots of *Hyptis comaroides* (syn. *Peltodon longipes*) against human pancreatic (MIAPaCa-2) and melanoma (MV-3) tumor cell lines (IC_{50} 1.9 and 2.9 μM respectively). This compound seems to exert its activity through alkylation mechanisms (Fronza et al., 2012).

A series of bioactive 5,6-dihydro-*α*-pyrones was isolated from a chloroform extract of *Hyptis brevipes.* The compounds brevipolides G – J (**177**–**180**) exhibited cytotoxic activity on a panel of cancer cell lines with ED_{50} of 0.3–8 μg/mL (Suárez-Ortiz et al., 2013). From the essential oil of *Medusantha martiusii* (syn. *Hyptis martiusii*), a LC_{50} of 263.12 μg/mL was found when tested against mammalian fibroblasts (ATCC and CCL-1) (de Figueirêdo et al., 2018). Moreover, the essential oil of *Cantinoa stricta* (syn. *Hyptis stricta*) showed cytotoxic action against a cancer breast cell line (MCF-7) (Scharf et al., 2016).

Finally, the essential oil from *Mesosphaerum sidifolium* (syn. *Hyptis umbrosa*) and its major component, fenchone (**253**), were tested against Ehrlich tumor cells implanted in the peritoneal cavity of female mice. The authors reported that the essential oil (100 and 150 mg/kg) and fenchone (**253**) (60 mg/kg) were able to reduce all analyzed parameters related to tumor (volume, mass and total viable cells). Furthermore, it was found that both treatments caused a blockage in the cell cycle progression (Rolim et al., 2017).

5.6. Other activities

Some Hyptidinae species have been evaluated for other activities such as antihyperglicemic, antihyperuricemic, antioxidant, anti-inflammatory, against snake venoms, effects on central nervous system, spasmolytic, to treat sepsis, interactions with cytochrome P-450 and antiacethylcholinesterase. The main results related to these activities are presented below.

5.6.1. Antihyperglycemic activity

A hydroethanolic extract (50%) from *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*) was assessed trough the streptozotocin model in order to verify its antihyperglycemic activity. A significant reduction in the rat blood glucose was observed in diabetic animals treated with the extract. This finding could be attributed to the stimulating effects on glucose utilization and antioxidant enzymes (Mishra et al., 2011). Using the same experimental model, Ogar et al. (2018) investigated the effect of ethanolic extract from the leaves of *Condea verticillata* (syn. *Hyptis verticillata)* and found interesting results such as significant decrease in body weight, increased fasting blood glucose and glycated hemoglobin levels, decreased pancreatic islet area and *β*-cell number, indicating an antihyperglycemic effect.

5.6.2. Antihyperuricemic activity

In subsequent studies with *Mesosphaerum suaveolens (syn. Hyptis suaveolens),* the antihyperuricemic effect of compounds isolated from its seeds was evaluated by xanthine oxidase inhibitory bioassay. The IC_{50} value comparable with the conventional drug allopurinol (IC_{50} 28.4 ± 1.1 mM) demonstrated that sodium 4,5-dicaffeoylquinate (**231**) (IC_{50} 69.4 ± 1.1 mM) and methyl 3,5-dicaffeoylquinate (**233**) (IC_{50} 92.1 ± 1.2 mM) could be potential compounds to be used in the treatment of hyperuricemia disease. Besides, the position of caffeoyl substitution could affect the inhibitory activity since 4,5 substitution have a higher effect than 3,5 (Hsu et al., 2019). These results are in line with the popular use of this species to treat urinary infection (Panda, 2014) and some renal disorders (de Santana et al., 2016).

5.6.3. Antioxidant activity

Natural antioxidants are widely distributed in food and medicinal plants. In this context, ethanolic and buthanolic extracts from aerial parts of *Condea undulata* (syn. *Hyptis fasciculata*) were evaluated concerning their antioxidant properties. The results demonstrated a DPPH radical scavenging activity higher than that obtained with *Ginkgo biloba,* a reference plant with well documented antioxidant activity (Silva et al., 2005). The extracts were also able to protect the eukaryotic microorganism *Saccharomyces cerevisiae* of the oxidative damage by hydrogen peroxide and menadione, a source of superoxide radical (Silva et al., 2009). Additionally, essential oils of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), *Hyptis rhomboidea* and *Hyptis brevipes* were tested in front of DPPH radical, being the better results obtained with *Hyptis brevipes* (main compounds *β*-caryophyllene (**262**), methyl eugenol (**254**) and 3-allylguaiacol (**255**)) with SC_{50} value of 2.02 μg/mL (Xu et al., 2013).

5.6.4. Anti-inflammatory activity

Regarding anti-inflammatory potential, the effects of a chloroform extract of *Condea albida* (syn. *Hyptis albida*) on inflammatory responses in mouse lipopolysaccharide (LPS) induced peritoneal macrophages were evaluated. The results demonstrated that the extract was able in inhibit LPS-induced production of TNF-α and interleukin-6, signaling molecules in the inflammatory cascade (Sánchez Miranda et al., 2013). Besides, the essential oil of *Cantinoa americana* (syn. *Hyptis spicigera*), whose main compounds were *α*-pinene (**238**), sabinene (**246**) and *β*-caryophyllene (**262**), was tested. Approximately 75% of lipoxigenase inhibition was achieved in the treatment with this oil (8 mg/mL) (Bayala et al., 2014).

5.6.5. Anti-snake venom activity

Approximately 14% of snake species worldwide are considered venomous, among them *Bothrops atrox* which is the species responsible for the most part of accidents in the Northern region of Brazil. The hemorrhagic, phospholipase A2 and proteolytic activities of *Bothrops* venoms have been associated with the pathogenesis of the lesions. In this context, crushed leaves and inflorescences, as well as infusions of *Marsypianthes chamaedrys* were tested against the venom of this snake species. The results demonstrated that infusion of inflorescences presents better results in the inhibition of phospholipase A2 than the antivenom. Besides, all samples present high anticoagulant activity in the presence of the *Bothrops atrox* venom. Moreover, crushed leaves and inflorescences demonstrated inhibition of inflammatory effects after the venom injection in mice (Magalhães et al., 2011). In the same context, Castro et al. (2003) demonstrated the inhibitory effects (IC_{50} around 10 mg/mL) of aqueous extract of the same species on the coagulation induced by several snake venoms (*Bothrops insularis, Bothrops neuwedii, Bothrops jararaca, Bothrops alternatus*). These results show the relevance of the popular knowledge since this species is widely used in the state of Amazonas (Northern Brazil) orally or as a poultice in the site of snakebites in order to relief the effects of the venom (de Moura et al., 2015).

Still addressing snake venoms, da Costa et al. (2008), demonstrated the antiedetamatogenic effect of ethanolic extracts from the flowers *of Hyptis radicans* (syn. *Peltodon radicans*) against *Bothrops atrox* using the mice paw edema model.

5.6.6. Activity on the central nervous system (CNS)

Central nervous system diseases are a group of neurological disorders that affect the function of the brain or spinal cord. Problems related to the nervous system include Parkinson disease, schizophrenia, epilepsy, central pain, depression, among others. The treatment is very important in order to avoid morbidity and mortality commonly associated with these infirmities.

In this sense, the potential of the essential oil from *Eplingiella fruticosa* in a model of Parkinson disease (reserpine) in mice was evaluated. In this study, a complexation of the oil with β-cyclodextrin was performed and the results demonstrated that the essential oil presents potential neuroprotective effect probably mediated by an antioxidant response. This effect was enhanced by the complexation with β-cyclodextrin, suggesting a novel technological approach to carry lipophilic samples (Beserra-Filho et al., 2019). In addition, behavior animal models were used to characterize the central effects of the essential oil from the leaves of *Medusantha martiusii* (syn. *Hyptis martiusii*) and its main component, 1, 8-cineole (**250**). The results suggest the essential oil presents an important hypnotic-sedative and antipsychotic-like effects, probably due to the presence of 1,8-cineole (**250**) (de Figuêiredo et al., 2019).

Still addressing activities on CNS, an aqueous extract of *Cantinoa americana* (syn. *Hyptis spicigera*) demonstrated anti-convulsant and sedative effects. The extract was capable of protecting 100 and 87.5% of mice against strychnine and pentylenetetrazol induced convulsions, respectively (160 mg/kg). In addition, the ability to increase total sleep duration induced by diazepam was also observed, representing a potent sedative effect (Bum et al., 2009). In addition, Almeida et al. (2018) evaluated the anti-acetylcholinesterase effect of the essential oil from the leaves of *Hyptis dilatata* obtaining inhibition rates higher than 96%.

5.6.7. Spasmolytic activity

Plant species are recognized by possess compounds with spasmolytic activity relieving cramps that are an important symptom of gastrointestinal disorders. In this context, the effect of an ethanolic extract from the aerial parts of *Leptohyptis macrostachys* (syn. *Hyptis macrostachys*) was assessed on smooth muscle models. The results demonstrated that the extract presented spasmolytic action (27–729 μg/mL) on guinea pig ileum, by blockage of calcium channels, in a concentration-dependent manner (de Souza et al., 2013). Furthermore, the α-pyrone hyptenolide (**191**) isolated from the aerial parts of the same species was also able to inhibit the contractions induced by carbachol or histamine in guinea pig ileum, demonstrating the spasmolytic activity of this compound (Costa et al., 2014).

5.6.8. Hepatoprotective activity in sepsis models

Among the various studies carried out with species of Hyptidinae there is an investigation of the effect of the essential oil of *Hyptis crenata* in models of liver dysfunction during early sepsis (Lima et al., 2018). Despite of continuous efforts concerning sepsis treatments, this condition remains as the main cause of deaths in the intensive care units. In the above-cited study, the sepsis was induced by the cecal ligation and puncture (CLP) experiments and the essential oil was administered 12 and 24 h after surgery (300 mg/kg). The outcomes from this study revealed that this essential oil played a protective effect against liver injury induced by sepsis.

5.6.9. Interactions with cytochrome P-450

More recently, the potential herb-drug interactions was assessed in order to verify the influence of some Hyptidinae species on the enzymatic complex cytochrome *P*-450. Picking et al. (2018) analyzed the impact of *Condea verticillata* (syn. *Hyptis verticillata*) extracts on activities of key cytochrome *P*-450 enzymes (CYPS 1A1, 1A2, 1B1, 3A4 and 2D60). The dried plant aqueous extracts showed potent inhibition on the activities of CYPS 1A1 (7.6 μg/mL), 1A2 (1.9 μg/mL), 1B1 (9.4 μg/mL). Furthermore, ethanolic extracts from dry and fresh plants demonstrated a potent inhibition of CYP1A2, in concentrations of 1.5 and 3.9 μg/mL, respectively. Other authors have demonstrated the inhibition of cytochrome *P*450 enzymes caused by an aqueous extract of *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), finding the subtype CYP1A2 (3.68 $\pm$ 0.10 μg/mL) as the least inhibited when compared to CYP2D6 (1.39 $\pm$ 0.01 μg/mL) and CYP3A4 (2.36 $\pm$ 0.57 μg/mL) (Thomford et al., 2018). Hence, care should be taken when these extracts are co-administered with drugs that are substrate to enzymes belonging to this complex.

5.7. Toxicity

Aiming to evaluate toxic effects of the essential oils of some Hyptidinae species, three samples were tested in the toxicity assay against *Artemia salina*. The results showed significant toxicity with median lethal concentration (LC_{50}) values of 62.2 $\pm$ 3.07 μg/mL, 65.9 $\pm$ 6.55 μg/mL and 60.8 $\pm$ 9.04 μg/mL to *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), *Hyptis rhomboidea* and *Hyptis brevipes* essential oils, respectively (Xu et al., 2013).

In another study, with *Mesosphaerum suaveolens* (syn. *Hyptis suaveolens*), the essential oil and the infusion of dry leaves were tested against *Drosophila melanogaster* and *Artemia salina*. The main components of the essential oil were β-caryophyllene (**262**) (18.6%), sabinene (**246**) (15.9%) and spathulenol (**291**) (11.1%) while the leaf infusion showed caffeic acid as the major constituent (12.76 mg/g). While the essential oil caused impairment of the locomotor behavior of flies and toxicity with LC_{50} of 15.5 and 49.2 μg/mL in *Drosophila melanogaster* and *Artemia salina*, respectively, the infusion had no effect in the organisms (Bezerra et al., 2017).

Rolim et al. (2017) evaluated the toxicity (mice erythrocytes, acute preclinical and genotoxicity) of the essential oil from *Mesosphaerum sidifolium* and its main component, fenchone (**253**). The results demonstrated that the essential oil induced weight loss, but presented no positive results in hematological, biochemical or histological parameters. On the other hand, fenchone (**253**) induced a decrease of hepatic enzymes, suggesting liver damage which could be a hindrance in the use of this compound in therapeutics.

Finally, Caldas et al. (2013) presented the low repeated dose toxicity of the essential oil of *Medusantha martiusii* (syn. *Hyptis martiusii*) in mice (100 and 500 mg/kg). This study was justified by the extensive use of this species in traditional medicine to treat gastric disorders. The results of this study demonstrated no toxicity signs or mice deaths along the 30 days as well as no differences in body weight gain.

6. Concluding remarks

Approximately 20 species of Hyptidinae have been cited in the ethnobotanical studies presented in this review. Besides the value as pest repellents, the main uses of these species are as wound healing and pain-relief agents, as well as for the treatment of diseases of the respiratory and gastrointestinal tracts. In these studies, the most cited species are *Mesosphaerum suaveolens*, *Mesosphaerum pectinatum*, *Cantinoa mutabilis* and *Hyptis crenata*. However, few studies have been conducted to evaluate their effectiveness and establish the nature of the active constituents. An exception is *Mesosphaerum suaveolens* that has been more extensively investigated in both ethno and experimental scientific approach and, as it can be seen in this review, the results corroborate some of the traditional use.

Chemical prospection on Hyptidinae indicated the occurrence of diterpenes, lignans, triterpenes, α-pyrones, flavonoids and phenolic acids. Essential oils have been reported for species of most genera. In this sense, some of them seem to have been used in folk medicine due to their essential oil content and proven biological activities of these compounds may justify a series of applications.

Although all classes of compounds found so far in the studied species have representatives endowed with relevant biological activities, special attention should be given to the presence of lignans in several plants of this subtribe. Up to now, they were found in species from seven genera, and 35 different compounds, including podophyllotoxin, have been isolated.

In addition to the fact that podophyllotoxin-type lignans have an unquestionable value as lead compounds for the development of the semisynthetic anticancer drugs teniposide and etoposide, their presence in some species could be related to the alleged therapeutic properties of the plants. Indeed, these compounds have been demonstrating a wide range of activities.

Biological evaluations conducted to date have shown that essential oils, extracts and compounds isolated from some species have activities such as repellent/insecticide, antimicrobial and cytotoxic. In addition, some species used in folk medicine to relieve various types of pain, against snake bites venoms and as leishmanicidal agents have had these activities confirmed.

Against this backdrop, even considering that relatively few species have been investigated from the chemical and pharmacological point of view, the available information indicates that the subtribe Hyptidinae is a fruitful source for future discoveries. In addition to the possibility of finding many important compounds, such as diterpenes and α-pyrones, according to the data collected in this review, the subtribe Hyptidinae appears as an alternative source of podophyllotoxin and closely related derivatives. Thus, there is a wide-open door for future investigations, both to support the popular uses of the plants and to find new compounds and activities in this large number of species not yet explored.

Authors' contribution

Henrique Bridi and Gabriela de Carvalho Meirelles contributed to literature searching and data collection in addition to the manuscript preparation and revision. Gilsane Lino von Poser contributed to the study concepts and design as well as manuscript preparation and revision. All the authors discussed, edited and approved the final version.

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