Journal of Ethnopharmacology 244 (2019) 111932

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

Ethnopharmacology, phytochemistry and pharmacology of the genus *Hedyosmum* (Chlorantaceae): A review

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ARTICLE INFO

Keywords:
Hedyosmum
Traditional uses
Phytochemistry
Pharmacology

ABSTRACT

Ethnopharmacological relevance: The genus *Hedyosmum* (family: Chloranthaceae) represents an interesting source of natural active compounds, and the 45 species of this genus are widespread in Central and South America and to a lesser extent Southeast Asia (southern China and western Malaysia). Several species are traditionally used in folk medicine. However, the data made available in recent years have not been organized and compared.

Aim of this review: The present study is a critical assessment of the state-of-the-art concerning the traditional uses, the phytochemistry and the pharmacology of species belonging to the genus *Hedyosmum* to suggest further research strategies and to facilitate the exploitation of the therapeutic potential of *Hedyosmum* species for the treatment of human disorders.

Materials and methods: The present review consists of a systematic overview of scientific literature concerning the genus *Hedyosmum* published between 1965 and 2018. Moreover, an older text, dated from 1843, concerning the traditional uses of *H. bonplandianum* Kunth has also been considered. Several databases (Francis & Taylor, Google Scholar, PubMed, SciELO, SciFinder, Springer, Wiley, and The Plant List Database) have been used to perform this work.

Results: Sixteen species of the genus *Hedyosmum* have been mentioned as traditional remedies, and a large number of ethnomedicinal uses, including for the treatment of pain, depression, migraine, stomach-ache and ovary diseases, have been reported. Five species have been used as flavouring agents, tea substitutes or foods. Sesterterpenes, sesquiterpene lactones, monoterpenes, hydroxycinnamic acid derivatives, flavonoids, and neolignans have been reported as the most important compounds in these species. Studies concerning their biological activities have shown that members of the *Hedyosmum* genus possesses promising biological properties, such as analgesic, antinociceptive, antidepressant, anxiolytic, sedative, and hypnotic effects. Preliminary studies concerning the antibacterial, antioxidant, antiplasmodial, and antifungal activities of these plants as well as their cytotoxic activities against different tumour cell lines have been reported. Some active compounds from the *Hedyosmum* genus have been used as starting points for the innovative and bioinspired development of synthetic molecules. A critical assessment of these papers has been performed, and some conceptual and methodological problems have been identified regarding the materials and methods and the experimental design used in these studies, including a lack of ethnopharmacological research.

Conclusions: The present review partially confirms the basis for some of the traditional uses of *Hedyosmum* species (mainly *H. brasiliense*) through preclinical studies that demonstrated their antinociceptive and neuroprotective effects. Due to promising preliminary results, further studies should be conducted on 13-hydroxy-8,9-dehydroshizukanolide and podoandin. Moreover, several essential oils (EOs) from this genus have been preliminarily investigated, and the cytotoxic and antibacterial activities of *H. brasiliense* and *H. sprucei* EOs certainly deserve further investigation. From the promising findings of the present analysis, we can affirm that this genus deserves further research from ethnopharmacological and toxicological perspectives.

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https://doi.org/10.1016/j.jep.2019.111932
Received 24 July 2018; Received in revised form 30 April 2019; Accepted 2 May 2019
Available online 22 May 2019

Abbreviations

DPPH, EOs	α,α-Diphenyl-β-picrylhydrazyl antioxidant activity assay, Essential Oils
GI_{50}, IC_{50}	Cell growth inhibition by 50%, Inhibitory concentration 50%
VERO	Green monkey kidney cells
MCF-7	Human breast cancer cells
THP-1	Human leukaemia monocyte cell line
A-549	Human lung carcinoma
DLD-1	Human colon adenocarcinoma
BQ-123	ETA antagonist (endothelin-1 ETA receptor)
13HDS	13-Hydroxy-8,9-dehydroshizukanolide
PDA	Podoandin
FST	Forced swimming test
ARD	Aromadendrane-4β,10α-diol
HDS	13-Hydroxy-8,9-dehydroshizukanolide
BHT	Butylhydroxytoluene
BHA	Butylhydroxyanisole
TEAC	Trolox equivalent antioxidant capacity (weak anti-tyrosinase)
A-549	Human lung cancer cell line
HL-60	Human leukaemia cells (tumour cell lines)
LD_{50}	Medium lethal concentration
HPTLC	High-performance thin-layer chromatography
MCF-7	Human breast cancer cell line
NSCLC	Non-small-cell lung cancer cells
NF-κB	Nuclear factor κB
PS-341	Inhibitor of the proteasome

1. Introduction

The genus *Hedyosmum* (Chlorantaceae) includes 48 species of small trees and shrubs (45 of which are taxonomically characterized and are *accepted* as species, and 3 species remain *unresolved*, meaning that they are not confirmed as *accepted* or *synonyms*) (The Plant List Database). The mentioned species are widespread in low and high mountain rain forests, such as the Andes of South America (Ecuador, Peru, Brazil, and central Bolivia) and the mountains of southern Mexico and Central America (Zhang et al., 2016; Guerrini et al., 2016). In America, *Hedyosmum* is the most abundant genus in the Chlorantaceae family (Kirchner et al., 2010). *H. orientale* has also been reported in China and West Malaysia. A common characteristic of these plants is their strong fragrance; indeed, the genus name finds its origin in the Greek words *hedy-* (sweet, nice, fragrant) and *osme* (smell). The Chlorantaceae family includes the genera *Sarcandra* (2 accepted species), *Chloranthus* (14 accepted species), *Hedyosmum* (45 accepted species) and *Ascarina* (12 accepted species). A common characteristic of this family, considered one of the most primitive among Angiospermae, is the presence of secretory cells in the stems and leaves (Kirchner et al., 2010; Eklund et al., 2004).

The genus is characterized by unisexual diclinous flowers and dentate and opposite leaves as well as petioles sheathed on the base (Todzia, 1988). The aerial parts (mainly the leaves but also bark and fruits) of species belonging to the genus *Hedyosmum* have been used in ethnomedical practices and traditional medicines, by South and Central American populations. Moreover, scientific studies concerning the chemical compositions of the different parts of these plants, which are all strongly aromatic, and the biological activities of the corresponding derivatives are continuously being published.

The aim of this review is to provide a critical analysis of the state-of-the-art concerning the ethnopharmacology, phytochemistry, pharmacology, and toxicology (with particular attention to cytotoxic effects) of the extracts and isolated compounds from the genus *Hedyosmum*. Moreover, the authors will suggest specific further studies that are needed and potential therapeutic applications of the *Hedyosmum* species for the treatment of human diseases.

2. Materials and methods

A detailed bibliographic study that included papers published from 1965 to 2018 was performed. Of the 112 documents evaluated at the beginning of this study, 50 references concerning ethnopharmacology data, phytochemistry and pharmacology studies of the genus *Hedyosmum* have been selected. Another 14 papers have been used to complete the present manuscript. Approximately 45 plant species were mentioned according to the classification given by the web page www.theplantlist.org, and 28 synonyms were identified. Three species remain unresolved, meaning that they are not yet accepted or confirmed as synonyms, and these assessments were made based on data obtained from theplantlist.org. The name of the genus, the scientific names of all the species belonging to genus *Hedyosmum*, and all the synonyms of the abovementioned scientific names were used as keywords. The present review was carried out using the following electronic databases: Francis & Taylor, Google Scholar, PubMed, SciELO, SciFinder, Springer, and Wiley. The authors have also checked the pharmacopoeias of Latin American and Central American countries, but no data concerning the genus *Hedyosmum* were found. Only articles were included, and data from symposiums, patents, and congress abstracts were avoided because the data from these sources were not complete enough to allow an effective comparison with the data from full papers. Due to the lack of data concerning traditional uses, some thesis works were initially considered but were discarded because they were considered unreliable from the scientific point of view.

3. Traditional uses

The oldest reference found by us during the present review is dated 1843, is written in Latin and mentions the traditional use of an *H. bomplandianum* leaf infusion as a febrifuge and analeptic remedy and as well as a treatment for hemicranias and pain caused by cold (Martius, 1843). The most relevant reference concerning the traditional uses of the genus *Hedyosmum* is the "Dictionary of Trees. Volume 2. South America. Nomenclature, Taxonomy and Ecology" (Grandtner and Chevrette, 2014). Eighteen species of the genus *Hedyosmum* were mentioned as medicinal remedies or food sources (beverages and fruits), and some species were also mentioned as sources of firewood and of construction materials. The most frequently reported traditional uses for the *Hedyosmum* genus are as sedatives, aphrodisiacs, and antidepressants and for treating stomach-ache. *H. angustifolium* has been used in the preparation of relaxing infusions and as a tea substitute. *H. anisodorum*, *H. arborescens*, *H. scaberrimus* and *H. scabrum* have mainly been reported as digestives, antispasmodics and stomach calmers, while *H. angustifolium*, *H. bonplandianum* and *H. racemosum* are used to soothing rheumatic and aching joint pains as well as fever and cold symptoms. The traditional uses of *H. colombianum* and *H. cumbalense* are mainly associated with human consumption as flavouring agents, and *H. sprucei* has been used in the treatment of snake bites.

The main traditional preparation in folk medicine is a pleasant tea (infusion) from the leaves, and this tea is consumed as a traditional remedy. Additionally, bark and fruits have been used in traditional medicinal preparations or as pleasant foods; in many cases, infusions of different *Hedyosmum* species have been described as aromatic beverages (Todzia, 1988). Examples of the preparation procedures concerning the traditional uses are quite limited. However, infusions of aerial parts are the most frequently mentioned folk medicine

Table 1
Ethnobotanical information regarding species belonging to the genus *Hedyosmum* with known traditional uses (botanical names and synonyms are reported according to The Plant List Database; http://www.theplantlist.org/).

Species	Synonyms	Traditional medicinal uses	Used part	Traditional preparation procedures	Distributions	Reference(s)
H. angustifolium (Ruiz & Pav.) Solms	*H. laciniatum* (Ruiz & Pav.) Solms *H. pavonii* (Solms) Diels *H. scabrum* var. *pavonii* Solms *Tafalla angustifolia* Ruiz & Pav. *Tafalla laciniata* Ruiz & Pav.	Antirheumatic, cold treatment	Leaves	NA	Bolivia	Lorenzo et al. (2006)
		Relaxing infusion, tea substitute	Leaves	Infusion	Ecuador, Peru, Bolivia	Grandtner and Chevrette (2014)
H. anisodorum Todzia	No synonyms (accepted species)	Treating stomach pain	Mature Fresh Leaves	Infusion	Ecuador	Todzia (1988)
		Infusion	Leaves	Infusion	Ecuador, Peru	Grandtner and Chevrette (2014)
H. arborescens Sw.	*H. elegans* Cordem. *Tafalla arborescens* (Sw.) Kuntze	Digestive aid, cold treatment, antispasmodic	Leaves	NA	Guadeloupe, French West Indies	Bercion et al. (2005)
H. bonplandianum Kunth	*H. callososerratum* Oerst. *Tafallaea bonplandiana* (Kunth) Kuntze *Tafallaea callososerrata* (Oerst.) Kuntze	Tranquilizer, hypnotic, analgesic, febrifuge	Leaves	NA	Panama, Colombia	Caballero-George et al. (2001) Cárdenas et al. (1993)
		Febrifuge, analeptic for the treatment of hemicranias and pain inflicted by cold	Leaves	Infusion	Brazil	Martius (1843)
		Febrifuge	Bark	NA	Nicaragua, Panama, Colombia, Ecuador	Grandtner and Chevrette (2014)
H. brasiliense Mart.	*H. acutifolium* Cordem. *H. grandifolium* Occhioni *H. weddellianum* Cordem. *Tafalla brasiliensis* (Miq.) Kuntze *Tafalla weddelliana* (Cordem.) Kuntze	Febrifuge, treating chills, and migraine pains, diuretic, stomach calmer, treating ovary diseases, treating rheumatism, sedative, antidepressant, hypnotic, aphrodisiac, foot fungi treatment, general refresher and substitute for green tea.	Leaves	Infusion	Central and South America, Brazil	Todzia (1988) Reitz (1965) Calixto et al. (2001) Trentin et al. (2015) Uphof (1968)
H. colombianum Cuatrec.	No synonyms (accepted species)	Odouriferous, flavouring substance in food	Leaves	NA	Colombia	Delgado et al. (2010)
H. costaricense C.E.Wood ex W.C.Burger	No synonyms (accepted species)	NA	NA	NA	NA	
H. crenatum	No synonyms (accepted species)	Infusion against flu	Leaves	Infusion	Colombia, Venezuela	Grandtner and Chevrette (2014)
H. cuatrecazanum Occhioni	*H. crassifolium* Urb.	Infusion against kidney illness, preparing aromatic beverages	Leaves	Infusion	Colombia, Venezuela, Ecuador, Perú, Bolivia	Grandtner and Chevrette (2014)
H. cumbalense	No synonyms (accepted species)	Flavouring agent	Leaves	NA	Central and South America	Todzia (1988)
		Treating stomach-ache	Leaves	Infusion	Colombia Ecuador, Perú	Grandtner and Chevrette (2014)
H. goudotianum Solms	*H. goudotianum* var. *goudotianum* *H. montanum* W.C.Burger *Tafallaea goudotiana* (Solms) Kuntze	Infusion against stomach-ache	Leaves	Infusion	Costa Rica, Panama, Colombia, Venezuela, Ecuador, Perú	Grandtner and Chevrette (2014)
H. luteynii Todzia	No synonyms (accepted species)	Infusion against kidney diseases	Leaves	Infusion	Colombia, Ecuador, Peru	Grandtner and Chevrette (2014)
H. maximum	No synonyms (accepted species)	Stimulant infusion	Leaves	infusion	Peru, Bolivia	Grandtner and Chevrette (2014)

(*continued on next page*)

Table 1 (*continued*)

Species	Synonyms	Traditional medicinal uses	Used part	Traditional preparation procedures	Distributions	Reference(s)
Hedyosmum mexicanum C.Cordem.	*H. artocarpus* Solms *Tafalla glauca* Ruiz & Pav. *Tafallaea artocarpus* (Solms) Kuntze *Tafallaea mexicana* (C.Cordem.) Kuntze	Food	Fruits, leaves	Infusion	Mexico, Panama, Colombia	Grandtner and Chevrette (2014)
H. nutans Sw.	No synonyms (accepted species)	Infusion with *Stenostomum lucidum* against colic	Leaves	Infusion	Guatemala, Belize, Honduras, Bahamas, Trinidad	Grandtner and Chevrette (2014)
H. orientale Merr. & Chun	No synonyms (accepted species)	NA	NA	NA	NA	
H. purpurascens Todzia	No synonyms (accepted species)	Food	Leaves	infusion	Ecuador	Grandtner and Chevrette (2014)
H. racemosum (Ruiz & Pav.) G.Don	*H. bolivianum* Cordem. *H. glabratum* Kunth	Treating aching joints	Leaves	Infusion for external use	Central and South America	Todzia (1988)
	H. glaucum (Ruiz & Pav.) C. Cordem.	Treating bronchitis	NA	NA	Perú	Bussmann et al. (2010)
	H. huilense Cuatrec. *H. integrum* Cordem. *H. llanorum* Cuatrec. *Tafalla integra* (Cordem.) Kuntze *Tafalla racemosa* Ruiz & Pav.	Medicinal infusion	Leaves	Infusion	Colombia, Venezuela, Guyana, Ecuador, Peru, Brazil, Bolivia	Grandtner and Chevrette (2014)
H. scaberrimum Standl.	No synonyms (accepted species)	Medicinal infusion	Leaves	Infusion	Nicaragua, Panama, Colombia, Ecuador	Grandtner and Chevrette (2014)
H. scabrum (Ruiz & Pav.) Solms	*H. hirsutum* Kunth	Stomach calmer, fertility promoter	Leaves	Infusion	Central and South America	Todzia (1988)
	H. latifolium Cordem.	Cold treatment, antirheumatic	Leaves	NA	Bolivia	Lorenzo et al. (2003)
	H. mandonii Solms *H. scabrum* var. *scabrum*	Antispasmodic	Leaves	Infusion	Peru	De Feo and Soria (2007)
	Tafalla mandonii (Solms) Kuntze *Tafalla scabra* Ruiz & Pav.	Infusion against stomach-ache	Bark and leaves	Infusion	Colombia Ecuador, Peru, Bolivia	Grandtner and Chevrette (2014)
H. scabrum var. *pavonii* Solms	*H. angustifolium* (Ruiz & Pav.) Solms	NA	NA	NA	NA	
H. scabrum var. *scabrum*	*H. scabrum* (Ruiz & Pav.) Solms	NA	NA	NA	NA	
H. sprucei Solms	*H. flocculosum* Diels *Tafalla sprucei* (Solms) Kuntze	Snake bites	Leaves	Cooked poultice for external use	Central and South America	Todzia (1988)
		Medicinal infusion	Leaves	Infusion	Colombia, Ecuador, Peru	Grandtner and Chevrette (2014)
H. translucidum Cuatrec.	*No synonyms (accepted species)*	Lemon-flavoured infusion	Leaves	Infusion	Colombia Venezuela, Ecuador, Peru	Grandtner and Chevrette (2014)
H. uniflorum Todzia	*No synonyms (accepted species)*	Medicinal infusion	Leaves	Infusion	Ecuador	Grandtner and Chevrette (2014)

NA – Not available.

preparations, and such preparations are ingested or topically applied. Home-distilled alcoholic beverages have also been reported as a traditional remedy. Reitz (1965) reported a traditional preparation procedure involving H. brasiliense, in which 30 g of fresh leaves are infused in 600 g of white wine, producing a tonic, which has aphrodisiac effects. Unfortunately, as shown in Table 1, no other detailed folk medicine procedures are reported, and the other reports only general discuss the part of the plant used or the extraction method, e.g., infusion or cooked poultice for external use. Currently, no data are available validating the traditional uses of *Hedyosmum* genus extracts, and no information has been reported in the pharmacopoeias of Latin American or Central American countries, despite being the areas of greatest distribution and use of this genus. Additionally, there are no scientific studies concerning the synergistic effects of these species with other species commonly used in the countries in which the *Hedyosmum* genus is widespread. One example is the traditional use of an infusion of *Stenostomum lucidum* and *H. nutans* for the treatment of colics. Unfortunately, no papers support this issue, and no data are available concerning the phytochemistry of *Stenostomum lucidum.* No data have been reported on the interactions of the *Hedyosmum* genus with prescribed medications. Finally, there are also very few ethnomedical data concerning the traditional preparation procedures or rituals, the part of the plant used, and the general traditional knowledge related to the *Hedyosmum genus*.

Traditional uses of members of the genus *Hedyosmum* in different countries are listed in Table 1.

Species of the genus *Hedyosmum* have various synonyms, as shown in Table 1, and they are widespread in several countries, as shown in Fig. 1. In addition, their common names are characteristic of the regions in which they are found. In Bolivia, *H. angustifolium* (Ruiz & Pavón) is called “Matico menta”, and in Brazil, *H. Brasiliense* is known as “cidrão", “cidreira” and “erva-de-bugre" among other names. In Colombia, the *H. translucidum* Cuatrec is known as “Granizo” or “Granicillo” because of the shape of its fruits. In Ecuador, *H. scabrum* is known as “Guayusa de cerro”, “Tarqui” or “Graniso” (De la Torre et al., 2008), and *H. sprucei* is known as “sacha limón panga”, " sacha limón caspa,” or " hoja de monte” (Guerrini et al., 2016).

4. Phytochemistry

The main chemical constituents of the *Hedyosmum* genus are listed in Table 2, and the chemical constituents of the essential oils (EOs) of *Hedyosmum* species are summarized in Table 3. The *Hedyosmum* genus offers several interesting and unique compounds, such as hedyosumins A, B, C, D, and E and hedyorienoids A and B. As reported by Trentin et al. (1999), 13-hydroxy-8,9-dehydroshizukanolide has been isolated from *H. brasiliense* and other plant species. Sesquiterpenes and sesterterpenes are the main focus of several studies concerning the biological activities of the *Hedyosmum* genus. Moreover, other interesting compounds, such as rosmarinic acid, have been reported to explain the biological activities of the *Hedyosmum* genus. Detailed information is provided in Section 5.

4.1. Sesquiterpenes and sesterterpenes

Sesterterpenes are the most commonly reported components in the *Hedyosmum* genus, and *H. brasiliense* is the most frequently mentioned species. The presence of seven sesquiterpenes, namely, guaianolide podoandin, 1,2-epoxy-10a-hydroxy-podoandin, 1-hydroxy-10,15-methylenepodoandin, elemenolide 15-acetoxy-isogermafurenolide, 15-hydroxy-isogermafurenolide, lindenanolide 8α/β,9α hydroxyl-onoseriolide and onoseriolide, in the species *H. brasiliense* was reported by Amoah et al. (2013). Onoseriolide was previously isolated from *H. angustifolium* bark by Acebey et al. (2010) together with other sesquiterpenes, such as oxyonoseriolide, hedyosmone, chloranthalactone A and spathulenol. Additionally, Su et al. (2008) reported the presence of spathulenol and other sesquiterpenes, such as 13-hydroxy-8,9-dehydroshizukanolide and aromadendrane-4β,10β-diol, in the ethanolic extract of the aerial parts of *H. orientale*. The sesquiterpene alcohol aromadendrane-4β,10α-diol was obtained from the leaves of *H. brasiliense* by Amoah et al. (2013a and 2015b). The mentioned compound was previously separated from other plant species, such as *Xylopia brasiliensis* (Moreira et al., 2003).

Amoah et al. (2013a; 2015b) reported eudesmane sesquiterpene lactones 1-α-acetoxyeudesma-3,7(11)–dien–8,12–olide and 15-hydroxy-isogermafurenolide from *H. brasiliense*. The sesquiterpene lactone 13-hydroxy-8,9-dehydroshizukanolide was also identified in a hydroalcoholic extract obtained from stems and leaves of *H. brasiliense* (Trentin et al., 1999; Calixto et al., 2001). Other sesquiterpene lactones, such as 7,10-epoxy-hedyosminolide and 7α,10α-epoxy-1α(H),5α(H)-guaia-3,11(13)-dien-8α,12-olide, were isolated from leaves of *H. arborescens* in Guadeloupe, French West Indies (Bercion et al., 2006). Su et al. (2008) isolated five guaiane-type sesquiterpenoids, hedyosumins A, B, C, D and E, for the first time from an ethanolic extract of the aerial parts of *H. orientale*. Additionally, two sesquiterpenoids, 10αR-hydroxy-1,5αRH-guaia-3,7(11)-dien-8αR,12-olide and 9αR-hydroxyasterolide,

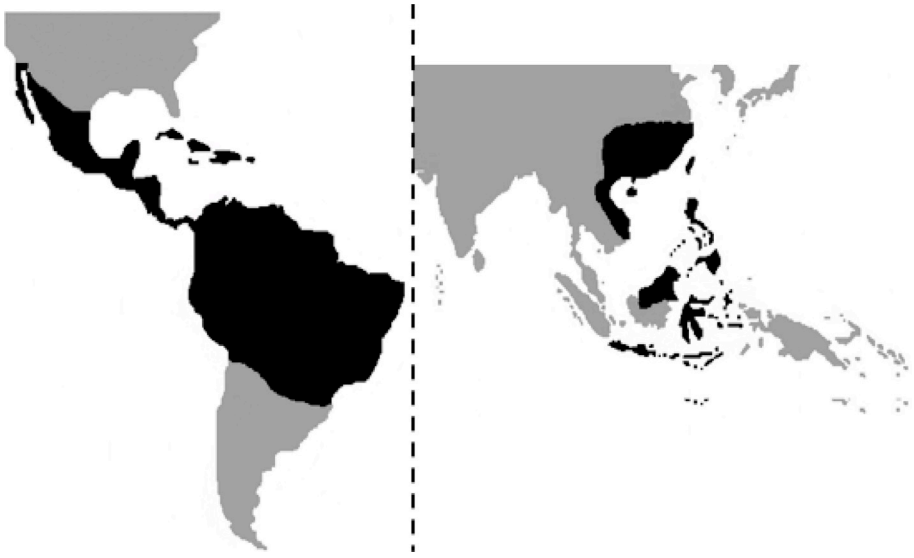


Fig. 1. Geographical distributions of the most abundant *Hedyosmum* species.

Table 2
Chemical constituents isolated and characterized from the most well-studied species belonging to the genus Hedyosmum (excluding essential oils).

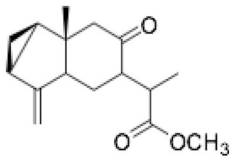
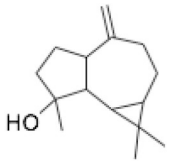
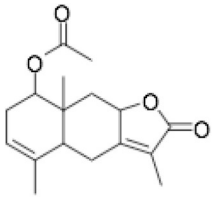
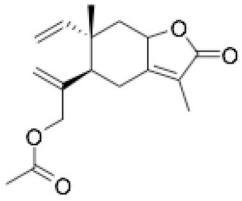
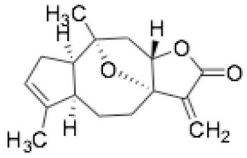
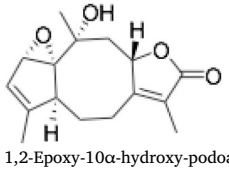
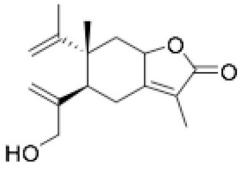
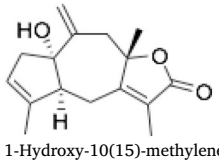
N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
1	 Hedyosmone	*H. angustifolium*	Stem bark/Ethyl acetate	Acebey et al. (2007, 2010)
2	 Spathulenol	*H. angustifolium* *H. Orientale*	Stem bark/Ethyl acetate Aerial parts/n.r.	Acebey et al. (2007, 2010) Zhang et al. (2016)
3	 1-α-Acetoxyeudesma-3,7(11)-dien-8,12-olide	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)
4	 15-Acetoxy-isogermafurenolide	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
5	 7α,10α-Epoxy-1α(H),5α(H)-guaia-3,11(13)-dien-8α,12-olide	*H. arborescens*	Leaves/Petrol ether Leaves/n.r.	Bercion et al. (2005, 2006) Zhang et al. (2016)
6	 1,2-Epoxy-10α-hydroxy-podoandin	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v) Leaves/n.r.	Amoah et al. (2013) Zhang et al. (2016)
7	 15-Hydroxy-isogerma-furenolide	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v) Leaves/Infusion	Amoah et al. (2013, 2015b)
8	 1-Hydroxy-10(15)-methylenepodoandin	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v) Leaves/n.r.	Amoah et al. (2013) Zhang et al. (2016)

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Table 2 (*continued*)

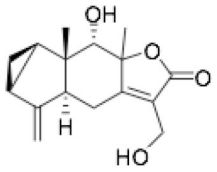
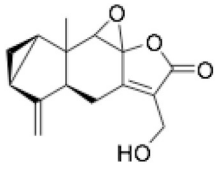
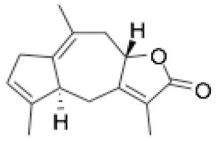
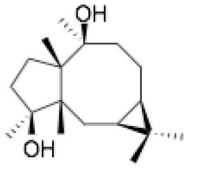
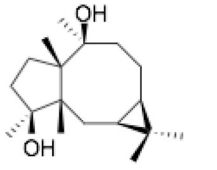
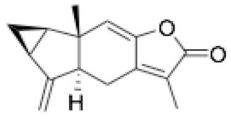
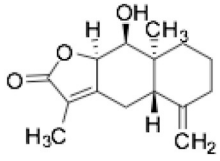
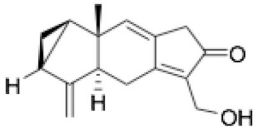
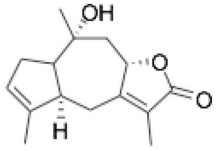
N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
9	 8α/β,9α-Hydroxyl-onoseriolide	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
10	 Oxyonoseriolide	*H. angustifolium*	Stem bark/Ethyl acetate	Acebey et al. (2007, 2010)
11	 Podoandin	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v) Leaves/Infusion Leaves/n.r.	Amoah et al. (2013, 2015a, 2015b) Zhang et al. (2016)
12	 Aromadendrane-4β,10α-diol	*H. brasiliense*	Leaves/Ethanol 95%	Amoah et al. (2015)
13	 Aromadendrane-4β,10β-diol	*H. orientale*	Aerial parts/Ethanol 95%	Su et al. (2008)
14	 Chloranthalactone A	*H. angustifolium*	Stem bark/Ethyl acetate	Acebey et al. (2007) Zhang et al. (2016)
15	 9αR-Hydroxyasterolide	*H. orientale*	Aerial parts/Ethanol 95%	Su et al. (2008), Zhang et al. (2016)
16	 13-Hydroxy-8,9-dehydroshizukanolide	*H. arborescens* *H. angustifolium* *H. brasiliense* *H. orientale*	Leaves/n.r. Stem bark/Ethyl acetate Leaves/EtOH–H_2O (95:5, v/v) Leaves/Infusion Aerial parts/n.r.	Calixto et al. (2001) Acebey et al. (2007, 2010), Zhang et al. (2016) Amoah et al. (2013, 2015a, 2015b), Zhang et al. (2016) Zhang et al. (2016)
17	 10αR-Hydroxy-1,5αH-guaia-3,7(11)-dien-8α,12-olide	*H. orientale*	Aerial parts/Ethanol 95% Aerial part/n.r.	Su et al. (2008), Zhang et al. (2016)

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Table 2 (*continued*)

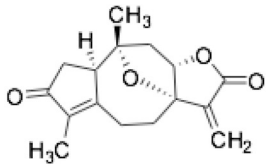
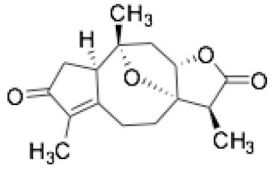
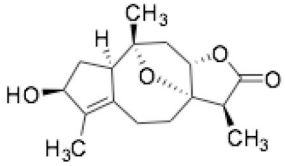
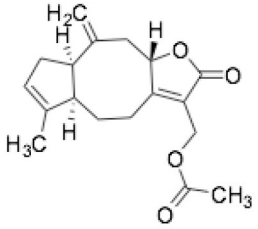
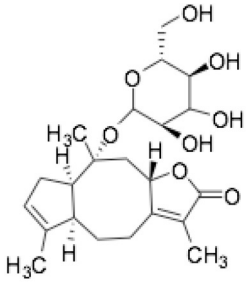
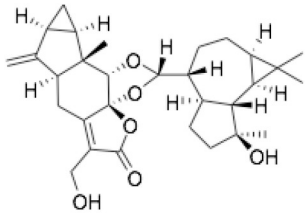
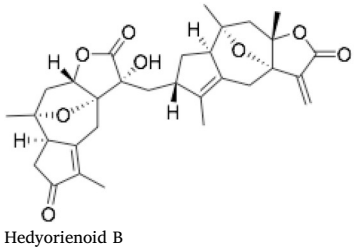
N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
18	 Hedyosumin A	*H. orientale*	Aerial parts/Ethanol 95% Aerial parts/n.r.	Su et al. (2008), Zhang et al. (2016)
19	 Hedyosumin B	*H. orientale*	Aerial parts/Ethanol 95% Aerial parts/n.r.	Su et al. (2008), Zhang et al. (2016)
20	 Hedyosumin C	*H. orientale*	Aerial parts/Ethanol 95% Aerial parts/n.r.	Su et al. (2008), Zhang et al. (2016)
21	 Hedyosumin D	*H. orientale*	Aerial parts/Ethanol 95% Aerial parts/n.r.	Su et al. (2008), Zhang et al. (2016)
22	 Hedyosumin E	*H. orientale*	Aerial parts/Ethanol 95% Aerial parts/n.r.	Su et al. (2008), Zhang et al. (2016)
23	 Hedyorienoid A	*H. orientale*	Twigs and leaves/Ethanol 95%	Fan et al. (2018)
24	 Hedyorienoid B	*H. orientale*	Twigs and leaves/Ethanol 95%	Fan et al. (2018)

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Table 2 (*continued*)

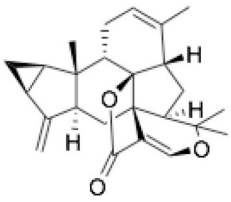
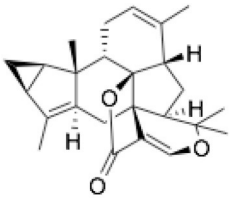
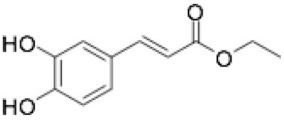
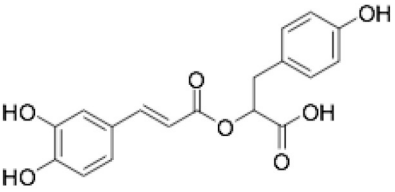
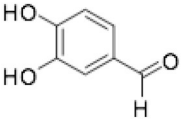
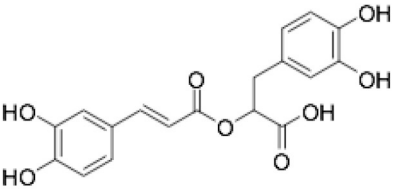
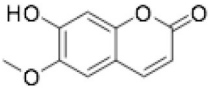
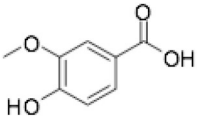
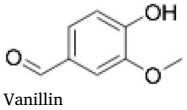
N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
25	 Bolivianine	*H. angustifolium*	Trunk bark/Ethyl acetate	Acebey et al. (2010)
26	 Isobolivianine	*H. angustifolium*	Stem bark/Ethyl acetate	Acebey et al. (2007, 2010)
27	 Ethyl caffeate	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
28	 Isorinic acid	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)
29	 Protocatechuin aldehyde	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
30	 Rosmarinic acid	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)
31	 Scopoletin	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
32	 Vanillic acid	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
33	 Vanillin	*H. brasiliense*	Leaves/EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)

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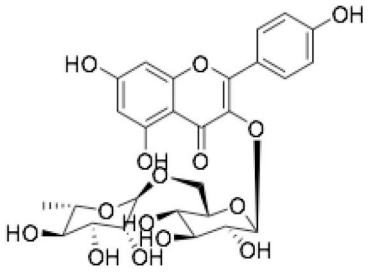
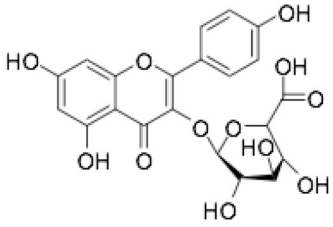
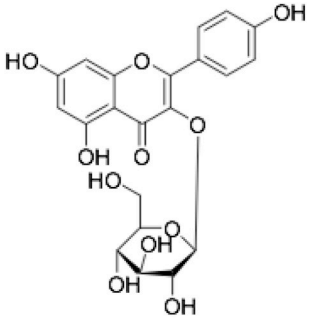
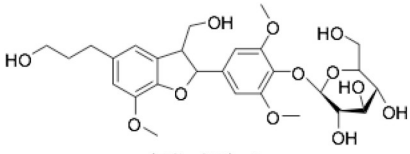
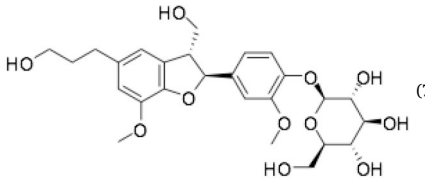
Table 2 (*continued*)

N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
34	 Kaempferol 3-O-[α-L-rhamnopyranosyl(1 → 6)-β-D-glucopyranoside]	*H. bonplandianum*	Leaves/Petroleum ether	Cárdenas et al. (1993)
35	 Kaempferol 3-O-β-D-glucuronide	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)
36	 Kaempferol 3-O-[β-D-glucopyranoside]	*H. bonplandianum*	Leaves/Petroleum ether	Cárdenas et al. (1993)
37	 (7S, 8R)-5-Methoxydihydrodehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)
38	 (7S,8R)-Urolignoside	*H. brasiliense*	Leaves/Infusion	Amoah et al. (2015b)

were isolated for the first time from natural sources. The prior compound was synthesized previously by Blay et al. (2000) from a santonin. Moreover, two sesquiterpenoid dimers, hedyorienoids A and B, were recently reported by Fan et al. (2018) and Tolardo et al. (2010), respectively. Finally, two sesterterpenes, bolivianine and isobolivianine, were isolated from an ethyl acetate extract of *H. angustifolium* (Acebey et al., 2010, 2007). These molecules have been widely investigated in the development of new techniques for organic synthesis.

4.2. Hydroxycinnamic acid derivatives

As reported by Amoah et al. (2015), rosmarinic acid and isorinic acid (caffeoyl-4′-hydroxy-phenyllactic acid) have been isolated from the fresh leaves of *H. brasiliense* by hot infusion; isorinic acid is considered an intermediate in the biosynthesis of rosmarinic acid. Rosmarinic acid is known to possess various biological activities, such as anticancer, neuroactive, and antioxidant activities (Amoah et al., 2015). Rosmarinic acid has recently been reported to be a hepatoprotective compound (Evidente et al., 2015) and as an effective prophylactic and remedy for neuropathic pain (Rahbardar et al., 2018). Moreover, another recent study performed by Cornejo et al. (2017) on rosmarinic acid showed a promising result concerning its ability to prevent fibrillization linked to Alzheimer's disease. A previous study from the same authors also mentioned the presence of another hydroxycinnamic acid derivative, ethyl caffeate (Amoah et al., 2013).

4.3. Flavonoids

A few reports are available on the flavonoids present in *Hedyosmum*, and this certainly represents a topic requiring further investigations in

Table 3
Main chemical components identified and characterized in the essential oils obtained from the most well-studied species belonging to the genus *Hedyosmum*.

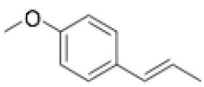
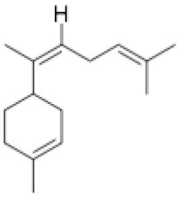
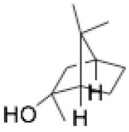
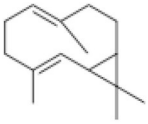
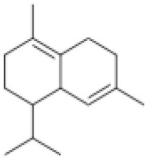
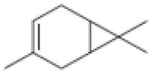
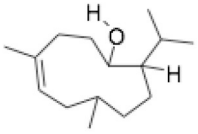
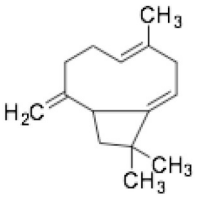
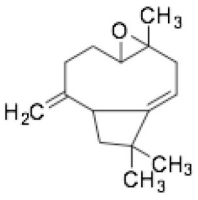
N.	Name and Structure	Species	Amount % (w/w)	Plant part	Ref.
39	 Anethole	*H. scabrum*	6.6%	Leaves	De Feo and Soria (2007)
40	 α-Bisabolene	*H. bonplandianum*	10.3%	Leaves	Mundina et al. (2000)
41	 Borneol	*H. glabratum*	6.8%	Leaves	Danis et al. (2012)
42	 Bicyclogermacrene	*H. arborescens*	10.6%	Leaves	Sylvestre et al. (2007)
43	 δ-Cadinene	*H. sprucei*	5.5%	Fresh aerial part	Guerrini et al. (2016)
44	 δ-3-Carene	*H. scabrum*	12.1%	Aerial part	Lorenzo et al. (2006)
45	 Carotol	*H. brasiliense*	9.8% 9.4% 6.5% 5.9%	Female flowers Male flowers Female leaves Male leaves	Murakami et al. (2017)
46	 β-Caryophyllene	*H. costaricensis* *H. translucidum* *H. sprucei*	6.1% 7.8% 15.5%	Leaves Leaves Fresh aerial part	Mundina et al. (2000), Zamora-Burbano and Arturo-Perdomo (2016) Guerrini et al. (2016)
47	 Caryophyllene oxide	*H. translucidum*	5.3%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
48	 1,8-Cineole	*H. angustifolium* *H. brasiliense* *H. scabrum*	3.7% 6.9% 4.6% 7.2% 10.8% 20.5%	Aerial parts Leaves from male plant Leaves from female plant Leaves from male flowers Leaves from male plant Leaves from female plant	Lorenzo et al. (2006) Murakami et al. (2017) Herrera et al. (2018)

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Table 3 (*continued*)

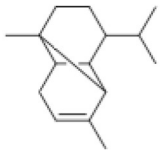
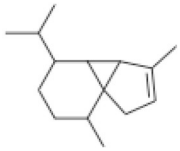
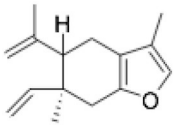
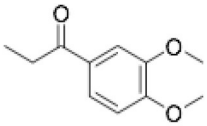
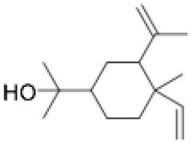
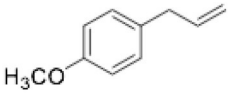
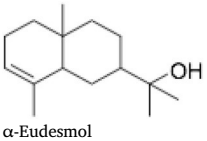
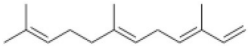
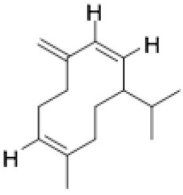
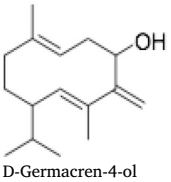
N.	Name and Structure	Species	Amount % (w/w)	Plant part	Ref.
49	 α-Copaene	*H. glabratum* *H. sprucei*	8.6% 5.1%	Leaves Fresh aerial part	Danis et al. (2012) Guerrini et al. (2016)
50	 α-Cubebene	*H. glabratum*	9.5%	Leaves	Danis et al. (2012)
51	 Curzerene	*H. brasiliense*	8.9%	Leaves	Kirchner et al. (2010)
52	 3′,4′-Dimethoxypropiophenone	*H. scabrum*	6.6%	Aerial part	Lorenzo et al. (2006)
53	 Elemol	*H. traslucidum*	5.8%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
54	 Estragole	*H. scabrum*	55.8%	Leaves	De Feo and Soria (2007)
55	 α-Eudesmol	*H. translucidum*	11.4%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
56	 (E,E)-α-Farnesene	*H. costaricence*	32.0%	Leaves	Mundina et al. (2000)
57	 Germacrene D	*H. scabrum* *H. sprucei* *H. translucidum* *H. costaricence*	13.0% 23.2% 8.9% 32.0%	Aerial parts Fresh aerial part Leaves Leaves	Lorenzo et al. (2006) Guerrini et al. (2016) Zamora-Burbano and Arturo-Perdomo (2016) Mundina et al. (2000)
58	 D-Germacren-4-ol	*H. scabrum*	12.6%	Leaves from male plant	Herrera et al. (2018)

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Table 3 (*continued*)

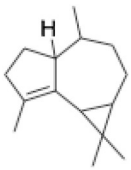
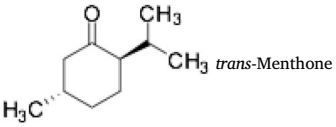
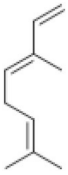
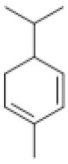
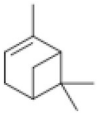
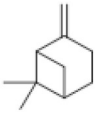
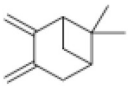
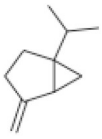
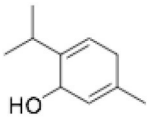
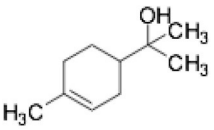
N.	Name and Structure	Species	Amount % (w/w)	Plant part	Ref.
59	 α-Gurjunene	*H. scabrum*	6.6%	Aerial part	Lorenzo et al. (2006)
60	 Linalol	*H. angustifolium* *H. scabrum*	6.1% 16.5%	Aerial parts Leaves from female plant	Lorenzo et al. (2006) Herrera et al. (2018)
61	 *trans*-Menthone	*H. mexicanum*	3.0%	Leaves	Mundina et al. (2000)
62	 (E)-β-Ocimene	*H. bomplandianum*	10.8%	Leaves	Mundina et al. (2000)
63	 α-Phellandrene	*H. arborescens* *H. brasiliense* *H. sprucei*	11.4% 8.1% 3.5%	Leaves Leaves from female flowers Fresh aerial parts	Sylvestre et al. (2007) Murakami et al. (2017) Guerrini et al. (2016)
64	 α-Pinene	*H. angustifolium* *H. scabrum* *H. scabrum* *H. scabrum*	24.0% 7.7% 6.4% 15.0%	Aerial parts Leaves Leaves from male plant Leaves from female plant	Lorenzo et al. (2006) De Feo and Soria (2007) Herrera et al. (2018) Herrera et al. (2018)
65	 β-Pinene	*H. angustifolium* *H. brasiliense* *H. colombianum* *H. mexicanum* *H. scabrum*	23.5% 5.2% 11.4–16.5% 4.6% 8.0% 4.8% 6.4%	Aerial parts Leaves from male plant Leaves Leaves Fruits Leaves from male plant Leaves from female plant	Lorenzo et al. (2006) Murakami et al. (2017) Delgado et al. (2010) Mundina et al. (2000) Mundina et al. (2000) Herrera et al. (2018)
66	 Pinocarvone	*H. brasiliense* *H. colombianum* *H. scabrum*	4.5% 3.2% 3.7% 8.4% 13.4% 14.2% 13.1%	Leaves from female plant Leaves from male flowers Leaves from female flowers Leaves Leaves Leaves from male plant	Murakami et al. (2017) Kirchner et al. (2010) Delgado et al. (2010) Herrera et al. (2018)
67	 Sabinene	*H. arborescens* *H. bomplandianum* *H. brasiliense* *H. mexicanum* *H. scabrum*	9.7% 14.7% 15.8% 15.8% 8.5% 9.5% 24.0% 24.6% 6.3%	Leaves Leaves Leaves from male plants Leaves from female plants Leaves from male flowers Leaves from female flowers Leaves Fruits Leaves from female plant	Sylvestre et al. (2007) Mundina et al. (2000) Murakami et al. (2017) Mundina et al. (2000) Herrera et al. (2018)
68	 Terpinen-3-ol	*H. bomplandianum* *H. mexicanum*	7.0%	Leaves Fruits	Mundina et al. (2000) Mundina et al. (2000)
69	 α-Terpineol	*H. brasiliense*	10.2%	Leaves	Kirchner et al. (2010)

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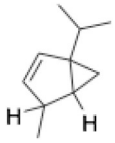
Table 3 (*continued*)

N.	Name and Structure	Species	Amount % (w/w)	Plant part	Ref.
68	 β-Thujene	*H. brasiliense*	7.1%	Leaves	Kirchner et al. (2010)

terms of both application and characterization. An early report by Cárdenas et al. (1993) described the isolation of two flavonoid glycosides, kaempferol 3-*O*-[*α*-L-rhamnopyranosyl(1 → 6)-*β*-D-glucopyranoside] and kaempferol 3-*O*-[*β*-D-glucopyranoside], from the n-butanol extracts of the leaves of *H. bonplandianum*. These findings are consistent with flavonoids being present in the folk medicines use as analgesics in Colombia. Rainer (2013) mentioned the antibiotic activity of a folk medicine involving *H. racemosum*, and the activity was probably due to the presence of flavonoids. Recently, Amoah et al. (2015) isolated kaempferol-3-O-β-*D*-glucuronide from *H. brasiliense*. The presence of this compound correlates well with the reported traditional uses (Table 1). Notably, kaempferol, a flavonoid, is a very important ingredient in functional foods and has a wide range of therapeutic applications, such as antioxidant, anti-inflammatory, and anticancer applications. Its action involves several intracellular and extracellular targets that regulate apoptosis, cell cycle, invasion or metastasis, angiogenesis, and inflammation. Further research to confirm its presence in other *Hedyosmum* species is encouraged.

4.4. Neolignans

Neolignans have attracted the attention of researchers due to the activity of the most well-known members of this class, magnolol and honokiol, which are the main substances responsible for the beneficial properties of magnolia bark extract. This very interesting class of molecules is still underexplored despite the initial interest and subsequent discovery of their potent antiplatelet activity (Shen, 1991). The neolignans (7S, 8R)-5-methoxydihydrodehydrodiconiferyl alcohol-4-O-*β*-D-glucopyranoside and (7S, 8R)-urolignoside were isolated from the fresh leaves *H. brasiliense* by Amoah et al. (2015). This is the first report of these compounds in the genus *Hedyosmum,* although they were previously found in other Chloranthaceae species, such as *Chloranthus japonicus* (Kuang et al., 2009) and *Sarcandra glabra* (Wu et al., 2012). Reports on neolignans in *Hedyosmum* are very rare, making them an interesting topic for further investigations.

4.5. Other compounds

Several other compounds have been detected in the n-hexane and EtOAc fractions of the hydro-alcoholic double-distillate of *H. brasiliense* (Amoah et al., 2013). The authors identified the phenolic aldehydes vanillin, protocatechuic aldehyde and 3,4-dihydroxybenzaldehyde, and the latter is a precursor in the biosynthesis of vanillin, which is an important compound. Coumarin scopoletin was also detected in this species.

4.6. Essential oils from the Hedyosmum genus

The *Hedyosmum* genus is also a source of essential oils (EOs). Several studies have been performed on different species and different parts of the plants, such as aerial parts, leaves, flowers, and fruits. Terpenes, including mainly sesquiterpenoids and monoterpenes, are the major constituents of EOs obtained by this genus. Table 4 summarizes the main compounds of *Hedyosmum* EOs. A large amount of data concerning EOs from the *Hedyosmum* genus have been reported over a considerable number of studies (Guerrini et al., 2016; Kirchner et al., 2010; Murakami et al., 2017; Correa-Royero et al., 2010). Two bicyclic monoterpenes, β-pinene and sabinene, are the most common constituents of *Hedyosmum* EOs and have been detected in 5 different species, followed by the sesquiterpene germacrene D (4 species), the isoprenoid pinocarvone and the cyclic monoterpene α-phellandrene (each in 3 species). β-Pinene has been reported to show promising antifungal activity against *Candida albicans* and a synergistic bactericidal effect against methicillin-resistant *Staphylococcus aureus* in combination with ciprofloxacin (Rivas da Silva et al., 2012). A study performed by Zhang et al. (2015) showed that β-pinene and paclitaxel have a synergistic effect against non-small-cell lung cancer cells (NSCLC). β-Pinene has also been reported as a component of several EOs; recent studies focused on Chinese traditional medicines have mentioned its analgesic and anti-inflammatory activities, its effectiveness for the control of *Rhodnius nasutus* (the vector of Chagas disease) (de Souza et al., 2018), and its potential as pest control agent against *Tribolium castaneum* (Pajaro-Castro et al., 2017). Additionally, sabinene, germacrene D and the other main components of *Hedyosmum* EOs have been extensively reported in several other studies concerning EOs.

4.7. Other related topics regarding the phytochemistry of the Hedyosmum genus

One of the principal findings of the reported studies is the active natural products, especially bolivianine, isobolivianine and onoseriolide, obtained from species belonging to the *Hedyosmum* genus. They have been used as starting points for innovative research toward bioinspired synthetic procedures (Yuan et al., 2013; Du et al., 2014; Ardkhean et al., 2016; Fan et al., 2016; Sun et al., 2016; Hugelshofer and Magauer, 2017; Li et al., 2017). Bioinspired approaches play a key role in discovery and constantly provide innovative avenues for studying new active compounds. It should be noted that sesterterpenes are unusual compounds that are often present in various marine organisms, especially sponges, but are also obtained from bacteria and plants. Sesterterpenes have been studied for their peculiar chemical structures and for their anticancer and cytotoxic activities (Kaweetripob, 2018; Evidente et al., 2015; Wang, 2012; Ebada, 2010).

5. Pharmacological effects

Ethnomedical practices and traditional uses of plants are often a source of inspiration and useful starting points for studies regarding various types of biological activities. This is the case for the *Hedyosmum* genus, as the related ethnomedical reports have been used as a guide for many biological investigations. In this section, several different biological activities related to the EOs, various extracts and isolated compounds belonging to various *Hedyosmum* species are listed and briefly described. Finally, although some papers reported data concerning chemical antioxidant assays (e.g., DPPH assay and β-carotene/linoleic acid bioassay), these results are not discussed herein because this information is not considered pharmacologically relevant. The antioxidant activity is a widespread test in phytochemical studies of the

Table 4
The main relevant reported biological activities of pure compounds from *Hedyosmum* species (excluding essential oils and crude extracts).

No. of compound	Model	Reported biological activities	Positive control	Negative control	Ref.
4	*In vivo*	Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 51.1 ± 11.6%, 26.0 ± 5.1%, 57.9 ± 5.5%, respectively (DRD: 10 nM to100 μM)	NA	Vehicle	Leitolis et al. (2016)
12	*In vivo*	Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400 pmol/mouse, checked after 7 days, with 1 mg/site of 3, MAC: NA)	NA	NA	Amoah et al. (2015a)
23	*In vitro*	NF-κB inhibitory activity with IC_{50} values of 5.34 ± 2.21 μM (DRD: 6 doses at a dilution ratio of 1:3, followed by stimulation with 10 ng/mL TNF-α, 6 h, MAC: NA; IC_{50} = 0.037 μM)	PS-341	NA	Fan et al. (2018)
15	*In vitro*	1. Cytotoxicity against A-549 cells *in vitro*, IC_{50} = 3.1 μM 2. Cytotoxicity against HL-60 cells *in vitro*, IC_{50} = 8.8 μM 50	Pseudolaric acid B (0.30 μM ag IC_{50} against A-549) Etoposide (0.20 μM against HL-60)	NA NA	Su et al. (2008)
16	*In vivo* *In vitro* *In vitro* *In vitro* *In vivo* *In vivo* *In vivo*	1. Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400 pmol/mouse, checked after 7 days, with 1 mg/site of 17, MAC:NA) 2. Anti-leishmanial activities, IC_{50} = 19.8 μM against *L. amazonensis* 3. Anti-leishmanial activities, IC_{50} = 20.9 μM against *L. infantum* 4. Anti-leishmanial activities, IC_{50} values between 24.3 μM and 29.1 μM against intramacrophagic form (*L. infantum*) (DRD: 24 h–96 h) 5. Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 90.1 ± 5.9%, 54.6 ± 5.9%, 49.5 ± 3.9%, respectively (DRD: 10 nM to100 μM) 6. Antinociception against acetic acid-induced writhing, 89 ± 2, 57 ± 4 and 52 ± 5% according to i.p., i.c.v., and i.t. routes, respectively, *in vivo* (DRD: intraperitoneally (3 ± 60 mg/kg), intracerebroventricularly or intrathecally (10 ± 100 mg/site) 30, 10, and 10 min before acetic acid injection, respectively) 7. Antinociception against capsaicin-induced licking; 60 ± 5, 94 ± 4, and 61 ± 5% when the compound was given i.p., i.c.v., or i.t., respectively (DRD: 3 ± 300 mg/kg, i.p.; 1 ± 100 mg/i.c.v., or 10 ± 100 mg/i.t; 30, 10, and 10 min before acetic acid injection, respectively).	NA Amphotericin B Pentamidine Amphotericin B, Pentamidine NA NA NA	NA NA NA NA Vehicle Vehicle i.p. (10 mL/kg), i.c.v. (5 mL/site), or i.t. (5 mL/site) Appropriate vehicle intraperitoneally (10 mL/kg), i.c.v. (5 mL/site), or i.t. (5 mL/site), 30, 10, and 10 min before capsaicin injection, respectively	Amoah et al. (2015a) Acebey et al. (2010) Trentin et al. (1999)
34	*In vivo*	Analgesic activities (writhing test, DRD: 80 and 40 mg/kg in water MAC: NA)	5 mg/kg morphine, 75 mg/kg diclofenac	Water	Cárdenas et al. (1993)
36	*In vivo*	Analgesic activities *in vivo* (writhing test, DRD: 80 and 40 mg/kg in water MAC: NA)	5 mg/kg morphine, 75 mg/kg diclofenac	Water	Cárdenas et al. (1993)
10	*In vitro*	1. Cytotoxicity against THP-1 cells, IC_{50} = 4.2 μM 2. Cytotoxicity against MCF-7 cells, IC_{50} = 23.8 μM	NA NA	NA NA	Acebey et al. (2010)
11	*In vivo* *In vivo* *In vivo*	1. Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400 pmol/mouse, checked after 7 days, with 1 mg/site of 30, MAC: NA) 2. Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 86.8 ± 8.0%, 46.6 ± 5.7%, 65.9 ± 7.3%, respectively (DRD: 10 nM to100 μM) 3. Antidepressant effect, significant reduction in immobility time (decrease to 51.67% compared with the control, *in vitro*; DRD: 10 mg/kg)	NA NA Imipramine (50 mg/kg)	NA Vehicle NA	Amoah et al. (2015a) Leitolis et al. (2016) Tolardo et al. (2010)

DRD, Dose range tested and duration; MAC, Minimal active concentration; NC, Negative control; PC, Positive control; NA, Not available.

Hedyosmum genus, but this type of test has been called into question for their inadequate transferability to clinical applications. There is little or no evidence that *in vitro* antioxidant activities can be directly correlated with human studies (Mimica-Dukić et al., 2016; HerbalEGram, 2018).

The pharmacological effects of members of this genus are summarized in Tables 4 and 5.

5.1. Neuroprotective, anxiolytic, antidepressant and sedative effects

Compounds isolated from *H. brasiliense* have been investigated *in vivo* as neuroprotective agents. Specifically, ARD (aromadendrane-4β,10α-diol), 13HDS (13-hydroxy-8,9-dehydroshizukanolide) and PDA (podoandin) significantly enhanced the Aβ1-42 peptide-induced memory impairment in the passive avoidance test, without increased adverse effects on locomotor activities (Amoah et al., 2015a). As reported by Tolardo et al. (2010), the ethanolic extract of *H. brasiliense* and a compound isolated from this extract, podoandin, were studied in a preliminary neuropharmacological screening and displayed anxiolytic, antidepressant, sedative and hypnotic activities that support the ethnobotanical information. A study performed by Gonçalves et al. (2012) demonstrated that the crude extract of *H. brasiliense* and PDA can induce an antidepressant-like effect in mice (forced swimming test - FST). In the same study, to better understand the biological mechanism of the antidepressant-like activity, the mice were pretreated with selective receptor antagonists to investigate the possible involvement of dopaminergic, GABAergic, noradrenergic, opioid, oxidonitrergic and serotonergic systems. The results suggest that the mechanism involves the dopaminergic, noradrenergic and serotonergic systems but not the GABAergic, oxidonitrergic and opioid systems.

5.2. Analgesic and antinociceptive effect

Cárdenas et al. (1993) studied the n-butanol extract of *H. bonplandianum* and two flavonoid glycosides, kaempferol 3-*O*-[α-L-rhamnopyranosyl(1 → 6)-β-D-glucopyranoside] and kaempferol 3-*O*-[β-D-glucopyranoside], extracted from the leaves. A preliminary *in vivo* study on mice showed that these materials exhibited significant analgesic activities, which is consistent with ethnobotanical reports from Colombian folk medicine practices. A previous test performed by Di Stasi et al. (1988) on the same species showed that the aqueous ethanol (50:50, v/v) extract had *in vivo* analgesic activity (writhing test); in this test, the extract was concentrated to allow the administration of 1 g/kg doses in mice.

In a study regarding the 4:1 ethanol-water extract of *H. brasiliense* stems and leaves, Trentin et al. (1999) demonstrated for the first time a dose-related antinociceptive effect in different types of chemical pain in mice at concentrations from 12.7 to 69 mg/kg. Additionally, the sesquiterpene lactone 13-hydroxy-8,9-dehydroshizukanolide (13HDS), isolated from the same species, showed antinociceptive activity. A further work by Martini et al. (2007) described the antinociceptive effects of several compounds from plants reported as useful in Brazilian folk medicine. The sesquiterpene 13HDS, isolated from the leaves and stems of *H. brasiliense*, was able (812 μM) to inhibit [^{3}H] glutamate binding and [^{3}H] glutamate uptake by synaptic vesicles *in vitro*.

5.3. Anti-erectile dysfunction effect

Leitolis et al. (2016) investigated the relaxant effects of two compounds, 13-hydroxy-8,9-dehydroshizukanolide (podoandin) and 15-acetoxy-isogermafurenolide (elemanolide), isolated from *H. brasiliense* and the effects of the hexane fraction of the ethanolic extract of the leaves (15 days) on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*. The results of this study support the aphrodisiac effects of *H. brasiliense* extracts and its components (ranging from 49.5 to 65.9% at 100 μM) reported in ethnobotanical studies (Reitz et al., 1965). These findings may open a new

Table 5
The main relevant biological activities of EOs obtained from *Hedyosmum* species.

EOs[a]	Reported biological activities	Positive control	Negative control	Ref.
H. arborescens	1. Cytotoxicity against DLD-1 (colon adenocarcinoma) cells, IC_{50} = 178 ± 9 μg/mL (DRD: increasing concentration of EO for 48 h)	NA	NA	Sylvestre et al. (2007)
	2. Cytotoxicity against A549 (human lung cancer) cells *in vitro*, IC_{50} = 158 ± 7 μg/mL (DRD: increasing concentration of EO for 48 h)	NA	NA	
H. brasiliense	1. Activity against human pathogenic Gram-positive bacteria *Staphylococcus aureus*, *Staphylococcus saprophyticus* and *Bacillus. subtilis* (agar dilution method) (DRD: from 2.5 to 0.078% (v/v) at 35 °C for 24 h, MAC: both 0.312% (v/v)	Vancomycin	Vehicle	Kirchner et al. (2010)
H. sprucey	1. Activity against human pathogenic bacteria, *Listeria grayi* (microdilution method) (DRD: 0.03 μL/mL to 2 μL/mL at 37 °C for 6 h and at 26 °C for 24 h, MAC: 250 μg/mL)	Thymol	Sterile medium	Guerrini et al. (2016)
	2. Activity against human pathogenic bacteria *Staphylococcus aureus* (microdilution method) (DRD: 0.03 μL/mL to 2 μL/mL, at 37 °C for 6 h and at 26 °C for 24 h, MAC: 1000 μg/mL)	Thymol	Sterile medium	
	3. Activity against phytopathogenic bacteria, *Clavibacter michiganensis* subsp. *nebraskensis* DSM 20400 (microdilution method) (DRD: 0.03 μL/mL to 2 μL/mL at 37 °C for 6 h and at 26 °C for 24 h, MAC: 62 μg/mL)	NA	Sterile medium	
	4. Cytotoxicity against MCF-7 (breast adenocarcinoma) cells, IC_{50} = 32.76 ± 4.92 and 33.64 ± 0.43 μg/mL after 48 and 72 h, respectively (DRD: 1–100 μg/mL for 24, 48, and 72 h)	NA	Sterile medium	
	5. Cytotoxicity against A549 (human lung cancer) cells *in*, IC_{50} = 44.05 ± 2.35 and 43.55 ± 2.80 μg/mL after 48 and 72 h, respectively (DRD: 1–100 μg/mL for 24, 48, and 72 h)	NA	Vehicle	
			Vehicle	

DRD, Dose range tested and duration; MAC, Minimal active concentration; NC, Negative control; PC, Positive control; NA, Not available.
[a] All the data concerning the bioactivities of the EOs were acquired from *in vitro* tests.

avenue for treating erectile dysfunction. The authors suggested that further studies involving cardiovascular diseases are needed despite the absence of ethnobotanical information.

5.4. Anticancer effect

Acebey et al. (2010) reported the cytotoxic effects of five sesquiterpenes, oxyonoseriolide, hedyosmone, onoseriolide, chloranthalactone A and spathulenol, isolated from the ethyl acetate extracts of the bark of *H. angustifolium*. A cytotoxic assay was performed *in vitro* on human breast cancer cells (MCF-7) and the human leukaemia monocyte cell line THP-1. Oxyonoseriolide displayed strong cytotoxicity against VERO cells but moderate cytotoxicity against MCF-7 and THP-1 cells (IC_{50} values 0.2 μM, 23.8 μM and 4.2 μM, respectively). As reported by Sylvestre et al. (2007), the cytotoxic activity of the EO obtained from the leaves of *H. arborescens* was tested against human lung carcinoma (A-549) and human colon adenocarcinoma (DLD-1) cell lines. The oil showed moderate anticancer activity against both cell lines, with GI_{50} values (concentration of the EO that inhibited cell growth by 50%) of 178 ± 9 μg/mL for DLD-1 and 158 ± 7 μg/mL for A-549.

The cytotoxic activities of ten guaiane-type sesquiterpenoids isolated from *H. orientale* were investigated by Su et al. (2008). All compounds were evaluated for their cytotoxic activities against human lung adenocarcinoma (A-549) and human leukaemia (HL-60) tumour cell lines. Only one of the above-mentioned molecules, 9α-hydroxyasterolide, exhibited moderate activities against both the A-549 and HL-60 cell lines (IC_{50} values of 3.1 μM and 8.8 μM, respectively). Fan et al. (2018) reported for the first time the presence of two sesquiterpenoid dimers, hedyorienoids A and B, and the latter showed promising NF-κB inhibitory activity. Additionally, *H. sprucei* EO showed remarkable cytotoxic activities against MCF-7 (IC_{50} values of 32.76 ± 4.92 ??g/mL and 33.64 ± 0.43 ??g/mL at 48 h and 72 h, respectively) and A549 (IC_{50} values of 44.05 ± 2.35 ??g/mL and 43.55 ± 2.80 ??g/mL at 48 h and 72 h, respectively) cell lines (Guerrini et al., 2016).

5.5. Antibacterial and anti-plasmodial effects

The *in vitro* inhibitory effects of the EO of *H. brasiliense* against six bacterial species (*Bacillus subtilis, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Staphylococcus saprophyticus*) and six fungal species (*Candida albicans, Candida parapsilosis, Microsporum canis, Microsporum gypseum, Trichophyton rubrum* and *Trichophyton mentagrophytes*) were investigated. The oil showed low activities against Gram-negative strains but expressed good antibacterial activities (MIC values from 0.125 to 2.5% v/v) against Gram-positive bacteria and human opportunistic pathogenic fungi and dermatophytes (Kirchner et al., 2010). Another study regarding sesquiterpenoids obtained from *H. brasiliense* was carried out by Amoah et al. (2013). This work started with the isolation of seven compounds (1,2-epoxy-10α-hydroxy-podoandin, 1-hydroxy-10,15-methylenepodoandin, 15-acetoxy-isogermafurenolide, 8α/β,9α-hydroxy-onoseriolide, podoandin, onoseriolide, and 15-hydroxy-isogermafurenolide), which were tested against isoniazid-sensitive *Mycobacterium tuberculosis* cultures. None of these sesquiterpene lactones showed anti-mycobacterial activities at the studied concentrations (1–30 μM).

A study of the infusions obtained from the fresh leaves of the female and male plants of *H. brasiliense* (Amoah et al., 2015a) focused on the antimicrobial activities of the infusion and its main components (rosmarinic acid, isorinic acid, (7S,8R)-5-methoxydihydrodehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside, (7S,8R)-urolignoside, podoandin, onoseriolide, 1-α-acetoxyeudesma-3,7(11)–dien–8,12–olide, 15-hydroxy-isogerma-furenolide, and kaempferol-3-O-β-*D*-glucuronide) against *Mycobacterium tuberculosis*. No significant activities were observed at concentrations ranging from 100 to 1.56 μg/mL. Murakami et al. (2017) evaluated the chemical composition as well as the antifungal and the antioxidant activities of *H. brasiliense* EOs. Four oils were obtained by hydrodistillation from the leaves and flowers of both male and female trees. The EO from female flowers showed consistent antifungal activities against *Cladosporium sphaerospermum* Penz and *Cladosporium cladosporioides*. The other EOs showed weaker activities. In 2010, Acebey et al. studied the anti-leishmanial activities, the cytotoxic effects and the antiplasmodial activities of five sesquiterpenes, oxyonoseriolide, hedyosmone, onoseriolide, chloranthalactone A and spathulenol, isolated from the ethyl acetate extracts of the bark of *H. angustifolium*. Onoseriolide was the main active compound against two axenically cultured amastigotes, *Leishmania amazonensis* (IC_{50} = 19.8 μM) and *Leishmania infantum* (IC_{50} = 20.9 μM). Intramacrophagic amastigotes were also tested, and the assay showed IC_{50} values between 24.3 μM and 29.1 μM. Onoseriolide also exhibited moderate antiplasmodial activity and weak cytotoxicity.

5.6. Other biological effects

The ethanolic extract of the leaves of *H. bonplandianum* has been investigated by radioligand-binding techniques to determine its inhibition of [3H] BQ-123 binding (endothelin-1 ETA receptor). The assay represents a preclinical model for the treatment of cardiovascular, mental, and feeding disorders as well as hypertension. In this *in vitro* model, bioactive compounds bind to G-protein-coupled receptor subtypes, which seem to be involved in the above-mentioned disorders. In a preliminary screening, the extract showed very high inhibitory activity, suggesting that is could open new research opportunities in the field of endothelin receptor antagonists. Correa-Royero et al. (2010) evaluated the antifungal activities and cytotoxic effects of 32 EOs on VERO cells. From this *in vitro* study, according to the criteria for cytotoxic activity set by the American National Cancer Institute (USA) for crude extracts (IC_{50} < 30 μg/mL), the EOs of *Hedyosmum* spp. (*scaberrium* and *racemosum*) were cytotoxic. These data are very important for identifying antifungal compounds with low toxicity profiles. Hedyorienoid B, a sesquiterpenoid dimer obtained from *H. orientale*, was tested to determine its ability to inhibit NF-κB, a key factor involved in anti-inflammatory processes, cell survival, apoptosis, and metabolic diseases. Compound 12 showed promising NF-κB inhibitory activity with an IC_{50} value of 5.34 ± 2.21 μM (Fan et al., 2018).

5.7. Critical assessments of the papers reviewed and final discussion

The papers reviewed herein have been critically assessed, and some conceptual and methodological problems have been identified, especially regarding their materials and methods and the experimental designs. The assessments were based on the recent guidelines for manuscript submission in the peer-reviewed pharmacological literature (Editorial/Biochemical Pharmacology, 2015; Mullane and Williams, 2015). For instance, none of the reviewed studies reported whether the investigator responsible for data analysis was blind to which samples or animals represented the control and treatment groups. None of the *in vitro* studies mentioned the passage number and population doubling time (PDL) of the cell lines used. Concerning the tests on animal models, only 3 reviewed papers mentioned complete data regarding compliance with regulations on the ethical treatment of animals, including the institutional committee or organization that approved the design of the experiments. Only one article reported data concerning the method of anaesthesia. Data on sex, weight, age and group size were adequately reported in 2 papers. Concerning the main relevant pharmacological data and the quantified results of concentration- and dose-response-related experiments (such as IC_{50} and/or EC_{50} values, the dose range tested, the minimal active concentration, *in vitro* or *in vivo* studies, positive and negative controls, experiment duration, and type of extract), a detailed description of the available data is presented in Tables 4 and 5 The threshold for statistical significance (P value) was

clearly indicated, and data were reported as the mean ± standard deviation (SD) of three or more independent experimental replications.

In addition to the evaluation based on the guidelines for manuscript submission in the peer-reviewed pharmacological literature, all the review papers have been further analysed concerning the following criteria to assess their quality and validity. (a) Is the study linked to the described local and traditional uses? (b) Are the local and traditional uses adequately described in peer review references? (c) Is botanical identification by experts is mentioned? (d) Is the study based on isolated compounds? Only 7 of the papers reviewed completely described the relationship between the study and the local and traditional uses or knowledge as well as presenting a solid methodology concerning botanical identification. In all the reviewed papers, traditional uses and ethnomedical information are poorly described or only partially reported. Moreover, especially in the older studies and in the evaluations of EOs, the pharmacological studies were performed only on crude extracts or fractions. Some gaps remain in the above-mentioned data related to conceptual and methodological approaches, especially regarding the material and methods sections of the reviewed papers. Further investigations on isolated compounds should be performed.

Finally, in order to summarize our results, the *Hedyosmum* genus appears to be an interesting platform for research into the large-scale use of plant species moving from ethnomedical traditions to possible applications in modern health products. Although many plants of the genus *Hedyosmum* have been reported to have important traditional uses, they are not mentioned in the pharmacopoeia of these countries, and studies are quite limited or incomplete. The most salient findings are studies on *H. brasiliense*, which is the most thoroughly investigated and mentioned plant of the genus, and some traditional uses reported for this species have been partially confirmed by *in vitro* and *in vivo* studies, even if solid clinical evidence remains far off. However, an important issue is that the traditional uses of preparations derived from *Hedyosmum* plants do not show relevant toxicological properties, supporting the fact that they can be considered generally recognized as safe; similar to other medicinal plants currently used in modern health products. In particular, preliminary studies on *H. orientale* and *H. sprucei* produced promising results, and notably numerous investigations (Martini et al. (2007); Tolardo et al. (2010); Gonçalves et al. (2012); Leitolis et al. (2016)) into their antidepressant activities and effects on erectile dysfunction suggest that they deserve further study. This framework highlights the importance of matching ethnobotanical and pharmacological studies to exploit the bioactivities related to human diseases for further modern applications. Traditional uses remain the largest clinical study ever conducted on medical plants, at least concerning their safety, and thus they constitute a good basis for the selection of novel active molecules for optimization with modern drug development approaches.

Although the traditional uses of 21 *Hedyosmum* species have been described, only 16 species (*H. angustifolium*, *H. anisodorum*, *H. arborescens*, *H. bonplandianum*, *H. brasiliense*, *H. crenatum*, *H. cuatrecazanum*, *H. cumbalense*, *H. goudotianum*, *H. luteynii*, *H. maximum*, *H. nutans*, *H. racemosum*, *H. scabrum*, *H. sprucei*, and *H. uniflorum*) of the genus *Hedyosmum* have been mentioned as traditional remedies, and a large number of ethnomedicinal uses have been reported, including for the treatment of pain, depression, migraine, stomach-ache and ovary diseases. Five species (*H. colombianum*, *H. mexicanum*, *H. purpurascens*, *H. scaberrimum*, and *H. translucidum*) have been reported as flavouring agents, as tea substitutes, infusions or foods. The preliminary findings described by Martini et al. (2007) allow the presumption of interactions between 13HDS (16) and other drugs that act on the glutamatergic system. Actually, as reported in the present review, the link between ethnobotanical and pharmacological studies passing through phytochemistry of *Hedyosmum* species seems to be at the beginning of the story, resulting in promising and interesting implications.

With specific reference to phytochemical evidence and applications, *Hedyosmum* species containing bolivianine, isobolivianine and onoseriolide are emerging as important starting points for developing bioinspired synthetic procedures and products. Moreover, the species *H. brasiliense* that contain 13-hydroxy-8,9-dehydroshizukanolide and rosmarinic acid, both known to exert relaxant, antinociception, and neuroprotective effects through *in vitro* and *in vivo* assays, may have applications in the treatment of Alzheimer's disease. Flavonoids, kaempferol derivatives and neolignans, in particular, are very important natural molecules with several health effects and applications, and the corresponding extracts from *Hedyosmum* genus seem to be underinvestigated.

The chemical constituents of the EOs from 11 species of the *Hedyosmum* genus have been investigated, but preliminary studies regarding biological activities have been reported for only 3 species and additional research is needed. In particular, the antibacterial bioautography-guided approach represents an interesting tool to rapidly and easily connect the phytochemistry and biological activities of phytocomplexes, as shown by Guerrini et al. (2016). Again, the EO of *H. brasilense* is the most investigated, but interesting preliminary results have been reported for the EO of *H. sprucei*, especially concerning its cytotoxic activity, which highlights the need for further in-depth investigations.

Based on the research collected in the present review, most of the pharmacological effects of *Hedyosmum* spp. compounds can be attributed to sesquiterpenes, sesterterpenes, and hydroxycinnamic acid. The findings reported in the present review mainly focus on the chemical characterization of pure compounds or EOs with different approaches and different levels of detail; moreover, biological analyses of *Hedyosmum* spp. derivatives are “limited” to *in vitro* and *in vivo* assays, and the data often do not adequately match the phytochemical investigations of the species. These findings encourage in-depth investigations focused on the *Hedyosmum* genus, as more studies reporting various useful biological activities and chemical compositions are undoubtedly of great interest in the medicinal chemistry and medical fields. Most of these studies were inspired by traditional ethnomedical practices carried out mainly by South and Central American populations.

6. Conclusion

Several research groups have investigated the *Hedyosmum* genus, and some promising preliminary findings have been reported. Despite this, there has not yet been sufficient follow-up to fully clarify these discoveries.

In order to expand our understanding and promote research on *Hedyosmum* species, the following approaches should be of interest to the research community: (1) recollect and systematize the traditional knowledge concerning *Hedyosmum* species for focused ethnopharmacological research; (2) design new studies concerning the semisynthesis or the partial chemical synthesis for the development of new bioactive chemical entities based on the bioactive compounds mentioned in Tables 5 and 13-hydroxy-8,9-dehydroshizukanolide (molecule 16) and podoandin (molecule 11) should perhaps be prioritized as they have been investigated more than the other molecules; (3) further investigate the use of *H. brasiliense* extracts, fractions or pure compounds as potential treatments of Alzheimer's disease; (4) screen the bioactivities of pure compounds from the EOs of the *Hedyosmum genus*, with the bioautography-guided approach as a privileged method; (5) perform toxicological evaluations (acute and long-term toxicity studies) given the lack of empirical and scientific data while considering the traditional knowledge derived from traditional long-term use; (6) more investigations are needed to elucidate the biosynthetic pathways, the pharmacodynamics, the pharmacokinetics, the mechanisms of action and the toxicities of compounds present in *Hedyosmum* spp.

Due to the importance of developing new bioactive compounds, this review provides a complete and up-to-date overview of traditional uses and scientific studies regarding the *Hedyosmum* genus and represents a

starting point for researchers who want to approach the study of these plants from new perspectives, revitalizing the scientific interest in this genus.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Author contributions

MR drafted the manuscript, coordinated the study and revised the final version. AT, AP, KDS, and PB participated in data mining, literature analysis, and manuscript editing. GS contributed to completing the taxonomical information and revised the final version. SM contributed to the conception of the study. SV and AB monitored the study, revised the manuscript and edited the final version. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

This research was supported by the Universidad Estatal Amazónica, Ecuador, and the University of Ferrara (FAR2017), Italy. We thank Dr. Nag Raju Maddela for comments that greatly improved the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2019.111932.

References

Acebey, L., Sauvain, M., Beck, S., Moulis, C., Gimenez, A., Jullian, V., 2007. Bolivianine, a new sesterpene with an unusual skeleton from *Hedyosmum angustifolium*, and its isomer. Isobolivianine. Org. Lett. 9 (23), 4693–4696. https://doi.org/10.1021/ol7015725.

Acebey, L., Jullian, V., Sereno, D., Chevalley, S., Estevez, Y., Moulis, C., Beck, S., Valentin, A., Gimenez, A., Sauvain, M., 2010. Anti-leishmanial lindenane sesquiterpenes from *Hedyosmum angustifolium*. Planta Med. 76 (04), 365–368.

Amoah Solomon, K.S., de Oliveira, F.L., da Cruz, A.C.H., De Souza, N.M., Campos, F.R., Barison, A., Biavatti, M.W., 2013. Sesquiterpene lactones from the leaves of *Hedyosmum brasiliense* (Chloranthaceae). Phytochemistry 87 (Suppl. C), 126–132. https://doi.org/10.1016/j.phytochem.2012.11.018.

Amoah Solomon, K.S., Dalla Vecchia, M.T., Pedrini, B., Carnhelutti, G.L., Gonçalves, A.E.G., dos Santos, D.A., Biavatti, M.W., de Souza, M.M., 2015a. Inhibitory effect of sesquiterpene lactones and the sesquiterpene alcohol aromadendrane-4β,10α-diol on memory impairment in a mouse model of Alzheimer. Eur. J. Pharmacol. 769 (Suppl. C), 195–202. https://doi.org/10.1016/j.ejphar.2015.11.018.

Amoah Solomon, K.S., Kouloura, E., Dutra, L.M., Barison, A., Wildner, L.M., Bazzo, M.L., Halabalaki, M., Skaltsounis, L.A., Biavatti, M.W., 2015b. Phytochemical analysis of the hot tea infusion of *Hedyosmum brasiliense*. Phytochemistry Lett 13 (Suppl. C), 267–274. https://doi.org/10.1016/j.phytol.2015.07.013.

Ardkhean, R., Caputo, D., Morrow, S.M., Shi, H., Xiong, Y., Anderson, E.A., 2016. Cascade polycyclizations in natural product synthesis. Chem. Soc. Rev. 45 (6), 1557–1569.

Bercion, S., Couppe de K/Martin, M.A., Baltaze, J.P., Bourgeois, P., 2005. A new α-methylene γ-lactone sesquiterpene from *Hedyosmum arborescens*. Fitoterapia 76 (7), 620–624. https://doi.org/10.1016/j.fitote.2005.06.006.

Bercion, S., Buffeteau, T., Lespade, L., Couppe de K/Martin, M.A., 2006. IR, VCD, ^{1}H and ^{13}C NMR experimental and theoretical studies of a natural guaianolide: unambiguous determination of its absolute configuration. J. Mol. Struct. 791 (1), 186–192. https://doi.org/10.1016/j.molstruc.2006.01.030.

Blay, G., Bargues, V., Cardona, L., Garcìa, B., Pedro, J.R., 2000. Stereoselective synthesis of 7,11-Guaien-8,12-olides from santonin. Synthesis of podoandin and (+)-Zedolactone A. J. Org. Chem. 65 (20), 6703–6707. https://doi.org/10.1021/jo000927h.

Bussmann, R.W., Malca-García, G., Glenn, A., Sharon, D., Chait, G., Díaz, D., Pourmand, K., Jonat, B., Somogy, S., Guardado, G., Aguirre, C., Chan, R., Meyer, K., Kuhlman, A., Townesmith, A., Effio-Carbajal, J., Frías-Fernandez, F., Benito, M., 2010. Minimum inhibitory concentrations of medicinal plants used in Northern Peru as antibacterial remedies. J. Ethnopharmacol. 132, 101–108. https://doi.org/10.1016/j.jep.2010.07.048.

Caballero-George, C., Vanderheyden, P.M.L., Solis, P.N., Pieters, L., Shahat, A.A., Gupta, M.P., Vauquelin, G., Vlietinck, A.J., 2001. Biological screening of selected medicinal Panamanian plants by radioligand-binding techniques. Phytomedicine 8 (1), 59–70. https://doi.org/10.1078/0944-7113-00011.

Calixto, J.B., Scheidt, C., Otuki, M., Santos, A.R.S., 2001. Biological activity of plant extracts: novel analgesic drugs. Expert Opin. Emerg. Drugs 6 (2), 261–279. https://doi.org/10.1517/14728214.6.2.261.

Cárdenas, L.C., Rodríguez, J., Villaverde, M.C., Riguera, R., Cadena, R., Otero, J.A., 1993. The analgesic activity of *Hedyosmum bonplandianum*: flavonoid glycosides. Planta Med. 59 (01), 26–27.

Correa-Royero, J., Tangarife, V., Durán, C., Stashenko, E., Mesa-Arango, A., 2010. In vitro antifungal activity and cytotoxic effect of essential oils and extracts of medicinal and aromatic plants against *Candida krusei* and *Aspergillus fumigatus*. Rev. Bras. de Farmacog. 20, 734–741.

Danis, M., Ávila, D., Ortega, J., Peña, N., Rojas, L., Cepeda, Y., 2012. Composición química del aceite esencial de *Hedyosmum glabratum*. Ciencia 20, 68–72 Número Especial.

De Feo, V., Urrunaga Soria, R., 2007. Composition of the Essential Oil of *Hedyosmum scabrum* (R. et P.) Solms (Chloranthaceae). J. Essent. Oil Bear. Pl 10 (1), 41–45. https://doi.org/10.1080/0972060X.2007.10643517.

De la Torre, L., Navarrete, H., Muriel, M.P., Macía, J., Balslev, H., 2008. Enciclopedia de las Plantas Útiles del Ecuador (con extracto de datos). Herbario QCA de la Escuela de Ciencias Biológicas de la Pontificia Universidad Católica del Ecuador & Herbario AAU del Departamento de Ciencias Biológicas de la Universidad de Aarhus, Quito, pp. 28–38.

De Souza de, A.T., Lopes, M.B.P., Ramos A, de S., Ferreira, J.L.P., Silva, J. R. de A., Queiroz, M.M.C., de Lima Araujo, K.G., Amaral, A.C.F., 2018. *Alpinia* essential oils and their major components against *Rhodnius nasutus*, a vector of Chagas disease. Hindawi Sci. World J. 6. Article ID 2393858. https://doi.org/10.1155/2018/2393858.

Delgado, P.A., Quijano, C.E., Morales, G., Pino, J.A., 2010. Composition of the essential oil from leaves and fruits of *Hedyosmum colombianum* Cuatrec., grown in Colombia. J. Essent. Oil Res. 22 (3), 234–236. https://doi.org/10.1080/10412905.2010.9700312.

Di Stasi, L.C., Costa, M., Mendaçolli, S.L.J., Kirizawa, M., Gomes, C., Trolin, G., 1988. Screening in mice of some medicinal plants used for analgesic purposes in the state of SãO Paulo. J. Ethnopharmacol. 24 (2), 205–211. https://doi.org/10.1016/0378-8741(88)90153-5.

Du, B., Yuan, C., Yu, T., Yang, L., Yang, Y., Liu, B., Qin, S., 2014. Asymmetric total synthesis of onoseriolide, bolivianine, and isobolivianine. Chem. Eur J. 20 (9), 2613–2622. https://doi.org/10.1002/chem.201304378.

Ebada, S.S., Lin, W.-H., Proksch, P., 2010. Bioactive sesterterpenes and triterpenes from marine sponges: occurrence and pharmacological significance. Mar. Drugs 8, 313–346. https://doi.org/10.3390/md8020313.

Eklund, H., Doyle, J.A., Herendeen, P.S., 2004. Morphological phylogenetic analysis of living and fossil Chloranthaceae. Int. J. Plant Sci. 165 (1), 107–151 January.

Evidente, A., Kornienko, A., Lefranc, F., Cimmino, A., Dasari, R., Evidente, M., Mathieu, V., Kiss, R., 2015. Sesterterpenoids with anticancer activity. Curr. Med. Chem. 22 (30), 3502–3522.

Fan, Y.-Y., Gao, X.-H., Yue, J.-M., 2016. Attractive natural products with strained cyclopropane and/or cyclobutane ring systems. Sci. China Chem. 59 (9), 1126–1141. https://doi.org/10.1007/s11426-016-0233-1.

Gonçalves, A.E., Bürger, C., Amoah, S.K.S., Tolardo, R., Biavatti, M.W., de Souza, M.M., 2012. The antidepressant-like effect of *Hedyosmum brasiliense* and its sesquiterpene lactone, podoandin in mice: evidence for the involvement of adrenergic, dopaminergic and serotonergic systems. Eur. J. Pharmacol. 674 (2), 307–314. https://doi.org/10.1016/j.ejphar.2011.11.009.

Grandtner, M.M., Chevrette, J., 2014. DICTIONARY of TREES. Volume 2. South America. Nomenclature, Taxonomy and Ecology. Elsevier, London.

Guerrini, A., Sacchetti, G., Grandini, A., Spagnoletti, A., Asanza, M., Scalvenzi, L., 2016. Cytotoxic effect and TLC bioautography-guided approach to detect health properties of amazonian *Hedyosmum sprucei* essential oil. Evid based complement. Altern. Med. 8. https://doi.org/10.1155/2016/1638342.

HerbalEGram, 2018. Volume 15 Issue 1. http://cms.herbalgram.org/heg/volume15/01January/JournalsSkepticalofAssays.html?ts=1541963546&signature=6178efd8d7be4fafc9ac6510c5ed541b.

Herrera, C., Morocho, V., Vidari, G., Bicchi, C., Gilardoni, G., 2018. Phytochemical investigation of male and female Hedyosmum scabrum (ruiz & pav.) solms leaves from Ecuador. Chem. Biodivers. 15 (2). https://doi.org/10.1002/cbdv.201700423.

Hugelshofer, C.L., Magauer, T., 2017. Bioinspired total syntheses of terpenoids. Org. Biomol. Chem. 15 (1), 12–16. https://doi.org/10.1039/C6OB02488B.

Kaweetripob, W., Mahidol, C., Tuntiwachwuttikul, P., Ruchirawat, S., Prawat, H., 2018. Cytotoxic sesterterpenes from Thai marine sponge *Hyrtios erectus*. Mar. Drugs 16, 474. https://doi.org/10.3390/md16120474.

Kirchner, K., Wisniewski Jr., A., Bella Cruz, A., Biavatti, M.W., Netz, D.J.A., 2010. Chemical composition and antimicrobial activity of *Hedyosmum brasiliense* Miq., Chloranthaceae, essential oil. Rev. Bras. Farmacogn. 20, 692–699.

Kuang, H-x, Xia, Y-g, Yang, B-y, Wang, Q-h, Lü, S-w, 2009. Lignan constituents from *Chloranthus japonicus* sieb. Arch Pharm. Res. (Seoul) 32 (3), 329–334. https://doi.org/10.1007/s12272-009-1303-1.

Leitolis, A., Amoah, S.K.S., Biavatti, M.W., da Silva-Santos, J.E., 2016. Sesquiterpene lactones from *Hedyosmum brasiliense* induce in vitro relaxation of rat aorta and corpus cavernosum. Rev. Bras. Farmacogn. 26 (3), 363–368. https://doi.org/10.1016/j.bjp.2016.01.005.

Li, J.-P., Yuan, C.-C., Du, B., Liu, B., 2017. An alternative total synthesis of bolivianine. Chin. Chem. Lett. 28 (1), 113–116. https://doi.org/10.1016/j.cclet.2016.06.013.

Lorenzo, D., Loayza, I., Dellacassa, E., 2003. Composition of the essential oils from leaves of two *Hedyosmum spp*. from Bolivia. Flavour Fragrance J. 18 (1), 32–35. https://doi.org/10.1002/ffj.1146.

Martini, L.H., Jung, F., Soares, F.A., Rotta, L.N., Vendite, D.A., dos Santos Frizzo, M.E., Yunes, R.A., Calixto, J.B., Wofchuk, S., Souza, D.O., 2007. Naturally occurring compounds affect glutamatergic neurotransmission in rat brain. Neurochem. Res. 32 (11), 1950–1956. https://doi.org/10.1007/s11064-007-9393-y.

Martius, K.F.P., 1843. Systema Materiae Medicae Vegetabilis Brasiliensis. Lipsiae,Vindobonae, Apud F. Fleischer; Apud F. Beck in Comm.
Moreira, I.C., Lago, J.H.G., Young, M.C.M., Roque, N.F., 2003. Antifungal aromadendrane sesquiterpenoids from the leaves of *Xylopia brasiliensis*. J. Braz. Chem. Soc. 14, 828–831.
Mundina, M., Vila, R., Tomi, F., Ciccio, J.F., Ibañez, C., Adzet, T., Casanova, J., Cañigueral, S., 2000. Composition of the essential oils from leaves and fruits of three *Hedyosmum* species from Costa Rica. Flavour Fragrance J. 15 (3), 201–205.
Murakami, C., Cordeiro, I., Scotti, M.T., Moreno, P.R.H., Young, M.C.M., 2017. Chemical composition, antifungal and antioxidant activities of *Hedyosmum brasiliense* mart. Ex miq. (Chloranthaceae) essential oils. Medicine 4 (3), 55. https://doi.org/10.3390/medicines4030055.
Pajaro-Castro, N., Caballero-Gallardo, K., Olivero-Verbel, J., 2017. Neurotoxic effects of linalool and β-pinene on *Tribolium castaneum* herbst. Molecules 22, 2052. https://doi.org/10.3390/molecules22122052.
Rainer, W.B., 2013. The Globalization of Traditional Medicine in Northern Peru.
Reitz, R., 1965. Clorantaceas - Flora Ilustrada Catarinense. Itajaí: Herbário "Barbosa Rodrigues". pp. 4–10.
Rivas da Silva, A.C., Lopes, P.M., Barros de Azevedo, M.M., Costa, D.C., Alviano, C.S., Alviano, D.S., 2012. Biological activities of alfa-pinene and ß-pinene enantiomers. Molecules 17 (6), 6305–6316. https://doi.org/10.3390/molecules17066305. May 25.
Shen, T.Y., 1991. Chemical and Biochemical Characterization of Lignan Analogs as Novel PAF Receptor Antagonists Lipids, vol. 26. pp. 1154–1156 12.
Su, Z.-S., Yin, S., Zhou, Z.-W., Wu, Y., Ding, J., Yue, J.-M., 2008. Sesquiterpenoids from *Hedyosmum orientale*. J. Nat. Prod. 71 (8), 1410–1413. https://doi.org/10.1021/np800240v.
Sun, W.-B., Wang, X., Sun, B.-F., Zou, J.-P., Lin, G.-Q., 2016. Catalytic asymmetric total synthesis of hedyosumins A, B, and C. Org. Lett. 18, 1219–1221. https://doi.org/10.1021/acs.orglett.6b00150.
Sylvestre, M., Pichette, A., Longtin, A., Couppe, M.A., Martin de, K., Bercion, S.R., Legault, J., 2007. Chemical composition of leaf essential oil of *Hedyosmum arborescens* and evaluation of its anticancer activity. Nat. Prod. Commun. 2 (12), 1269–1272.
The Plant List Database, 2013. The plant list. Version 1.1. http://www.theplantlist.org/ Accessed 1st November 2017.
Todzia, C.A., 1988. Chloranthaceae: Hedyosmum. Flora Neotropica. pp. 1–138.
Tolardo, R., Zetterman, L., Bitencourtt, D.R., Mora, T.C., Lazzarotto de Oliveira, F., Biavatti, M.W., Amoah, S.K.S., Bürger, C., de Souza, M.M., 2010. Evaluation of behavioral and pharmacological effects of *Hedyosmum brasiliense* and isolated sesquiterpene lactones in rodents. J. Ethnopharmacol. 128 (1), 63–70. https://doi.org/10.1016/j.jep.2009.12.026.
Trentin, A.P., Santos, A.R., Guedes, A., Pizzolatti, M.G., Yunes, R.A., Calixto, J.B., 1999. Antinociception caused by the extract of *Hedyosmum brasiliense* and its active principle, the sesquiterpene lactone 13-hydroxy-8, 9-dehydroshizukanolide. Planta Med. 65 (06), 517–521.
Uphof, J.C. Th, 1968. Dictionary of Economic Plants, second ed. Verlag von J. Cramer.
Wang, L., Yang, B., Lin, X.-P., Zhou, X.-F., Liu, Y., 2012. Sesterterpenoids. Nat. Prod. Rep. (30), 455–473.
Wu, H., Hu, X., Zhang, X., Chen, S., Yang, J., Xu, X., 2012. Benzyl 2-β-Glucopyranosyloxybenzoate, a new phenolic acid glycoside from *Sarcandra glabra*. Molecules 17 (5), 5212.
Yuan, C., Du, B., Yang, L., 2013. Bioinspired total synthesis of bolivianine: a diels–alder/intramolecular hetero-diels–alder cascade approach. J. Am. Chem. Soc. 135, 9291–9294.
Zamora-Burbano, A.M., Arturo-Perdomo, D.E., 2016. Composición química del aceite esencial de hojas *Hedyosmum translucidum* Cuatrec., Chloranthaceae (Granizo). Bol. Latinoam. Caribe Plantas Med. Aromat. (BLACPMA) 15 (3), 192–198.
Zhang, Z., Guo, S., Liu, X., Gao, X., 2015. Synergistic antitumor effect of α-pinene and β-pinene with paclitaxel against non-small-cell lung carcinoma (NSCLC). Drug Res. 65, 214–218. https://doi.org/10.1055/s-0034-1377025.
Zhang, M., Liu, D., Fan, G., Wang, R., Lu, X., Gu, Y., Shi, Q.-W., 2016. Constituents from Chloranthaceae plants and their biological activities. Heterocycl. Commun. 22 (4), 175–220. https://doi.org/10.1515/hc-2016-0084.