Journal of Medicinal Plant Research

Volume 11 Number 33, 3 September, 2017

ISSN 1996-0875

Academic Journals

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Journal of Medicinal Plants Research

Table of Contents: Volume 11 Number 33 3 September, 2017

ARTICLE

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Vol. 11(33), pp. 518-537, 3 September, 2017
DOI: 10.5897/JMPR2017.6412
Article Number: 7B3C12565868
ISSN 1996-0875

http://www.academicjournals.org/JMPR

Journal of Medicinal Plants Research

Review

The genus *Calea* L.: A review of isolated compounds and biological activities

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Received 3 May, 2017; Accepted 14 July, 2017

The approximately 125 species of the genus *Calea* L. (Asteraceae) are distributed throughout tropical and subtropical regions of the America. Some of the species have medicinal properties. Based on popular knowledge, different phytochemical and pharmacological activities have been the focus of research. This review aims to provide an overview of the current state of knowledge of medicinal uses, chemical constituents, and pharmacological activities of *Calea* species. Phytochemical and pharmacological studies have been performed on 37 species to date. Aerial parts, leaves and stems of these plants have been tested for several biological effects including antinociceptive, vasodilator, cytotoxic and antimicrobial activities. Extracts obtained from plants of the genus *Calea* have also been assayed for potential antiparasitic effects, especially for antiplasmodial, leishmanicidal, acaricidal and trypanocidal activities. Phytochemical investigations have confirmed that *Calea* species are rich in sesquiterpenes, chromenes, chromanones, flavonoids and other chemical compounds less attractive from the point of view of molecular diversity. This review confirms that certain *Calea* spp. enjoy widespread popular use in the treatment of infections, and the observed antiparasitic activities can provide new insights for further investigations on isolated compounds.

Key words: Medicinal plants, Sesquiterpene lactones, *Calea*.

INTRODUCTION

The Asteraceae family includes about 1,600 genera and 23,000 species around the world, which occur mostly in subtropical and tropical regions (Fernandes and Ritter, 2009). *Calea* L. is a large genus of this family (tribe Heliantheae Cass., subtribe Melampodiinae Less.) (Nascimento et al., 2002) containing approximately 125 species, distributed in tropical and subtropical regions of the Americas (Kadereit and Jeffrey, 2007; Roque and Carvalho, 2011). The genus ranges from Mexico through Central America into South America (Woodson Jr et al.,

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1975).

Saslis-Lagoudakis et al. (2014), claim that an important point for change in history is the ability of humans to learn from others and transmit this knowledge to those who live around them, thus ensuring the transmission and conservation of information. In the context of medicinal plant use, this is no different, as traditional knowledge is usually transmitted orally and associated with families, communities or ethnic groups (Hamilton, 2004; Abbet et al., 2014). So it is important to report literature on the traditional uses of medicinal plants.

Although, many species within the genus *Calea* are used in folk medicine, only a few studies have reported their efficacy. Due to the common use of *Calea* species in folk medicine, coupled with the fact that the genus has some species with proven biological activity in previously published articles, this review was meant to consolidate known data within. The scope of this article is to review compounds isolated from the genus *Calea* and their biological activities.

METHODOLOGY

A selection of relevant data was made through a search using the keyword "*Calea*" in "Scopus", "Google Scholar", "Web of Science", "PubMed", "ScienceDirect" and Scifinder databases. About 167 articles were found with the word *Calea* for inclusion. In this review, search terms "Calea and biological activity" and "Calea and phytochemistry" were further used. In total, 96 publications describing the biological activity of extracts, fractionated extracts or isolated compounds from species of the genus Calea were used, excluding articles solely on botany and agronomy. The isolated compounds were categorized by species in Table 1 and biological activities were discussed by pathology. Reported biological activities include those of isolated compounds in addition to those of crude and fractionated extracts. Plant taxonomy was validated using the databases of Brazilian Flora and information about popular use and botany was obtained from published books and academic documents.

MORPHOLOGICAL DESCRIPTION OF THE GENUS *Calea*

Species of the genus *Calea* include perennial herbs, sometimes with woody xylopodia and tuberous roots, subshrubs, shrubs and sometimes scandent to vine-like or small trees. Their leaves can be opposite, rarely alternate, verticillate or basal, with blades linear to ovate. Flowers feature as solitary inflorescences named capitula. The ray florets are pistillate, with ligulate corollas, commonly yellow and rarely whitish. The disc florets are bisexual, with tubular corollas, also predominantly yellow, and less commonly white or purplish. The fruits are obconical or obpyramidal cypselae, black or brown, glabrous or densely pubescent sometimes glandular (Baker, 1884; Kadereit and Jeffrey, 2007).

USE IN FOLK MEDICINE

Species of the genus *Calea* have been widely used in traditional medicine throughout their geographical range.

Calea glomerata Klatt has been described in Colombian folk medicine as an antihypertensive (Guerrero et al., 2002). In Mexican folk medicine, *Calea integrifolia* (DC.) Hemsl. is used as a hypoglycemic (Andrade-Cetto, 2015). In a Peruvian Amazonian ethnic group (Yanesha), *Calea montana* Klatt is used for skin infections and this was validated through testing for leishmanicidal activity; users apply onto infected wounds the mashed fresh leaves as a poultice (Valadeau et al., 2009). *Calea serrata* Less. popularly known as "erva-de-cobra", "chá-amargo" and "quebra-tudo", is an endemic species found in Southern Brazil (Ribeiro et al., 2008). It is used in traditional medicine to treat ulcers and liver problems (Camilotti et al., 2014) while also featuring in African-Brazilian religious rituals. Avancini and Wiest (2008) reported that *C. serrata* is popularly used in southern Brazil for skin diseases in humans and animals. *Calea uniflora* Less., commonly known as arnica-da-praia in the Southern region of Santa Catarina State, Brazil, has popular therapeutic indications including as an anti-inflammatory, analgesic, in the treatment of hematomas, as an antiseptic (for mosquito bites), for rheumatism, treatment of urinary infections and flu (Ramos et al., 2016).

Another species of the genus *Calea* used as a medicinal plant is *Calea pinnatifida* (R. Br.) Less., popularly known as "aruca","cipó-cruz" or "quebra-tudo" (Mors et al., 2000). This species is used in folk medicine for treating digestive disorders, giardiasis and amoebiasis (Machado Filho, 1930; Prusk and Urbatsch, 1988; Mors et al., 2000). *Calea urticifolia* DC. is also used by the Mayans in Mexico to treat gastroenteritis, oliguria and dysuria (Pereira and Pereira, 2002; Balam, 2008).

Calea hypoleuca Rob. & Greenm, is used by the Zapotec indigenous group of the Ocotlan district, within Mexico. In this context, the main use is postpartum, using the cooked leaves (decoction) in the form of baths.

One species of this genus with several indications is *Calea zacatechichi* Schltdl., known as 'white bitter herb' by Mixe, and 'bitter gum' by Popoluca peoples, inhabiting two areas in the Mexican states of Oaxaca and Veracruz, respectively, while both belonging to the Macro-Mayan linguistic stock. Within these populations, this plant is used for gastrointestinal purposes (stomach-ache, diarrhoea), dermatological/respiratory ailments (cough, asthma), and gynaecological indications by the Popoluca people; and gastrointestinal purposes (stomach-ache) and fevers by the Mixe people (Leonti et al., 2003). The

rural people of Oaxaca, Puebla and Veracruz also use this plant to treat diabetes and biliary diseases (Zamora-Martinez, 1992). It is also used in Mexico as an "anti-diabetic" (Ramos et al., 1992) and as an antiplasmodial in El Salvador (Köhler et al., 2002). Pereira and Pereira (2002) describes *C. zacatechichi* among Mayan medicinal flora for use in gastroenteritis, dermatitis, diarrhea and fever.

PHYTOCHEMISTRY

About 256 different compounds have been isolated and identified from *Calea* species with the aerial parts most thoroughly investigated. Of 257 compounds isolated from species of *Calea*, 116 are sesquiterpene lactones, 18 derived from *p*-hydroxyacetophenone, 14 phenolic compounds, 10 chromenes, 8 flavonoids, 7 benzofurans, and 5 chromanones. In this review, the inclusion of compounds has been based on chemical diversity. Such diversity is of primary interest for medicinal chemistry (Table 1).

Many reported constituents are sesquiterpene in character (Ober et al., 1985b, c, d, 1984a, 1984b, 1984c; Ohguchi et al., 2009; Carvalho et al., 2014; Martinez et al., 1987b; Bohlmann et al., 1984, 1982f, e, d, c, b, a, 1981b, a; Fischer et al., 1984; Lee et al., 1982a, 1982b; Vichnewski et al., 1982; Quijano et al., 1979; Herz and Kumar, 1980; Bohlmann and Jakupovic, 1979; Bohlmann and Zdero, 1977b). Also documented are essential oils (Carvalho et al., 2014), chromenes, chromanones and flavonoids (Lima et al., 2015a, b; Nascimento and Oliveira, 2014; Nascimento et al., 2007a; Ober et al., 1985b; Steinbeck et al., 1997) (Table 1).

Sesquiterpenoids are compounds containing 15 carbons, formed biosynthetically from three five-carbon isoprene units or may be synthesized industrially from monoterpenoid building blocks (Bauer et al., 1997). These secondary metabolites have significant roles in plants as deterrents against herbivores (Picman, 1986) and as anti-fungal and anti-bacterial allelopathic agents. Although the biological activities of these metabolites have not been completely elucidated as yet, anthelmintic, antibiotic, cytotoxic (Anke et al., 1989) and antiparasitic activities are known.

This review confirms that several *Calea* species traditionally utilized in folk medicine for the treatment of inflammation and various infections may serve as a bio-bank for the isolation of potential phytopharmaceuticals and act as leads in drug discovery. Collation of research reports on *Calea* and other plants is vital for a better understanding of how to develop rational therapeutics from ethnobotanical medicines.

A great number of natural compounds belonging to several families are present in the genus *Calea*. The most common are sesquiterpene lactones and chromenes. Nevertheless, chromanones and flavonoids are also represented in this genus. Unfortunately, few papers about the activity of chromanones are available.

Many natural compounds contain a chromene moiety, including tocopherols and flavonoids. Structural skeletons of chromane, *2H*-chromene and *4H*-chromene have in common the same benzofuran nucleus; of these, *2H*-chromene compounds are predominantly found in the genus *Calea.* Such *2H*-chromenes are known as antifungal compounds and some derivatives showed potential antidiabetic and antihypertensive activities as Na^+-glucose co-transporter inhibitors and potassium-channel activators, respectively (Thomas and Subin, 2013). They have also been revealed as efficient anti-inflammatory compounds, acting as selective inhibitors of cyclooxygenase- 2 (Wang et al., 2010) and of tumor necrosis factor α (TNF-α) production (Thomas and Subin, 2013). Mechanistically, no single mechanism of action is defined for these compounds as antimicrobial agents. Some chroman and chromene derivatives have exhibited DNA gyrase inhibition, and within the chromanones, a hydrogen bond donor/acceptor functionality at the 4-position together with a lipophilic 2-alkyl moiety is believed to be important for antibacterial activity. Much interest has focused on the use of chromenes as antiparasitic agents, with chromen/chroman-4-ones suggested to exert their effects through pteridine reductase 1 (PTR1) inhibition within both *Trypanosoma brucei* and *Leishmania* species (Di Pisa et al., 2017).

Sesquiterpene lactones are a large group of over 5000 compounds and they are particularly abundant in plants of to the Asteraceae family, including the genus *Calea*. They are characterized by 15-carbon terpenoids consisting of three isoprene units and a lactone ring, with some having an α-methylene-γ-lactone motif with an exo-cyclic double bond conjugated with a carbonyl function (Zhang et al., 2005). Six skeletons of sesquiterpenoids termed germacranolides, eudesmanolides, guaianolides, pseudoguaianolides, xanthanolides and carabranolides can be found in plants. In the genus *Calea,* germacranolides, eudesmanolides and guaianolides in particular are found (Ferreira et al., 1980; Ober et al., 1984d; Ortega et al., 1989). The α-methylene-γ-lactone group is responsible for most of their biological effects via a Michael-type addition. Parthenolide is a representative sesquiterpene lactone of the anti-tumor agents largely described for this family. Nevertheless, several are in clinical or pre-clinical stages and one, arglabin, is actually used as anticancer drug in Kazakhstan. They exert their effects on the nuclear factor NF-κB but also on the redox equilibrium of malignant cells (Gach et al., 2015). Analogously with chromenes, they also exhibit anti-inflammatory effects, notably those of the guaianolide family (Chadwick et al., 2013), with NF-κB involved through regulation of about 150 inflammatory genes. Besides already discussed antimicrobial effects, we can cite the antimalarial activity of artemisinin, whose activity is ascribed to the presence of an endoperoxide

Table 1. Species of the genus *Calea* used in traditional medicine and an overview of their isolated compounds.

Species name	Distribution	Plant materials	Chemical compounds isolated	Compound number	References
Calea angusta S.F.Blake	Brazil	Air-dried plant material	11,13-Dihydro-11,13-epoxyatripliciolide-2-methylbutyrate 9α-Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-2-methylbutyrate	*C*1 *C2*	Bohlmann et al. (1982d)
Calea berteriana DC.	Colombia	Air-dried plant material	Acacetin Calbertolide C Desacyl-8-tiglylsubcordatolide A 8-Epi-8-tiglylrupicolin A 8-Epi-8-tiglylrupicolin B	*C*3 *C*4 *C5* *C6* *C7*	Ober et al. (1985b)
	Venezuela	Dried leaves	Calebertin Calbertolide A Calbertolide B	*C8* *C9* *C10*	Ober et al. (1985a)
		Aerial parts	7-*O*-(α-L-Rhamnopyranosyl-(1-2)-β-D-glucopyranosyl)- 30,40,7-trihydroxyflavone	*C11*	Nascimento and Oliveira (2007b)
Calea clausseniana Baker	Brazil	Underground parts	Uniflorol A acetate Uniflorol B acetate 2,2-dimethyl-6-{1-[(4'-acetoxy)angeloyloxy]ethyl}chroman-4-one 2,2-Dimethyl-6-(1-hydroxyethyl)-chroman-4-one 2-Senecioyl-4-[1-(angeloyloxy)ethyl]phenol 2-Senecioyl-4-[1-(acetylsarracinoyloxy)-ethyl]phenol	*C12* *C13* *C14* *C15* *C16* *C17*	Nascimento and Oliveira (2014)
Calea clematidea Baker	Paraguay	Leaves, Flowers	Clemateol *o*-Vanillin Spathulenol α-Terpinene Germacrene Yomogi alcohol β-Caryophylene *m*-Cymene *o*-Cymene α –Gurjunene	*C18* *C19* *C20* *C21* *C22* *C23* *C24* *C25* *C26* *C27*	Flach et al. (2002)
Calea crocinervosa Wussow, Urbatsch & G.A.Sullivan	Mexico	Aerial parts	Crocinervolide	*C28*	Ortega et al. (1989)
Calea cuneifolia DC.	Brazil	Air dried xylopodium	1,1'-Bis-[2-senecionyl-4-(1-ethyl)-phenoxy]ether Meso-1,1'-Bis-[2-senecionyl-4-(1-ethyl)-phenoxy]ether 2-Senecionyl-4-vinylphenol	*C29* *C30* *C31*	Lourenço et al. (1981)

Table 1. Cont'd.

			2-Senecionyl-4-(1-hydroxyethyl)-phenol	*C32*	
			2-Senecionyl-4-(1-acetoxyethyl)-phenol	*C33*	
			2-Senecionyl-4-(1-acetylsarracinoyloxyethyl)-phenol	*C34*	
			2-(3-Methyl-3-hydroxybutanoyl-1)-4-(1-hydroxyethyl)-phenol	*C35*	
			6-Hydroxy-2,2-dimethylchroman-4-one	*C36*	
			Acetylsarracinic acid	*C37*	
Calea fruticosa (Gardner) Urbatsch, Zlotsky & Pruski.	Brazil	Leaves	α-Pinene	*C38*	Carvalho et al. (2014)
			p-Cymene	*C39*	
			Limonene	*C40*	
			Lavender lactone	*C41*	
			cis-Arbusculone	*C42*	
			trans-Arbusculone	*C43*	
			Linalool	*C44*	
			cis-Linalool oxide	*C45*	
			trans-Linalool oxide	*C46*	
			Terpinen-4-ol	*C47*	
			p-Cymen-8-ol	*C48*	
			trans-Carveol	*C49*	
			Carvone	*C50*	
			-Elemene	*C51*	
			Cyclosativene	*C52*	
			α-Copaene	*C53*	
			β-Bourbonene	*C54*	
			β-Cubebene	*C55*	
			β-Elemene	*C56*	
			(E)-Caryophyllene	*C57*	
			β-Copaene	*C58*	
			α-Humulene	*C59*	
			allo-Aromadendrene	*C60*	
			Dauca-5,8-diene	*C61*	
			β-Selinene	*C62*	
			epi-Cubebol	*C63*	
			α-Murolene	*C64*	
			-Cadinene	*C65*	
			Cubebol	*C66*	
			trans-Calamenene	*C67*	
			(*E*)-Nerolidol	*C68*	
			Spathulenol	*C20*	
			Caryophyllene oxide	*C69*	
			Gleenol	*C70*	

Table 1. Cont'd.

			Globulol	*C71*	
			Humulene epoxide II	*C72*	
			Junenol	*C73*	
			1-epi-Cubenol	*C74*	
			α-Murolol	*C75*	
			α-Cadinol	*C76*	
			Selin-11-en-4-α-ol	*C77*	
			cis-Calamenen-10-ol	*C78*	
			Eremophilone	*C79*	
Calea harleyi H. Rob.	Brazil	Air-dried plant material	8-Desacylacetylchapliatrin angelate	C80	Bohlmann et al. (1984)
			Calerhaloide-8-O[2',3'-epoxy-2'-methylbutyrate]	C81	
			Calerhaloide-8-O[ent-2',3'-epoxy-2'-methylbutyrate]	C82	
			Calerhaloide-8-O[2'-hydroxy-2'-methyl-but-3'-enoate]	C83	
Calea hispida (DC.) Baker	Brazil	Air-dried plant material	1,2-Dihydroxy- 3,4-dehydromenthone	*C84*	Bohlmann et al. (1982f)
			5β-Myrtenyl-9α-hydroxy-4,5-dihydroatripliciolide-8-*O*-angelate	*C85*	
			5β,9α-Dihydroxy- 4,5-atripliciolide-8-*O*-angelate	*C86*	
			15-Acetoxy-5-hydroxyfarnesyl acetate	*C87*	
			15-Acetoxy-5,10-dihydroxy-12,13-dehydro-10,11-dihydrofarnesyl acetate	*C88*	
Calea hymenoleps Baker.	*NR	Air-dried plant material	8-*O*-Dihydrocaleteucrin acetate	*C89*	Bohlmann et al. (1982c)
			Calelepin senecioate	*C90*	
			Caleahymenone A	*C91*	
			Caleahymenone B	*C91*	
			Isoatripliciolide angelate	*C93*	
			Caleamyrcenolide	*C94*	
Calea integrifolia (DC.) Hemsl.	Mexico		Heptadeca-2-*t*-9,16-trien-1-al	*C95*	Bohlmann and Zdero (1977a)
Calea jamaicensis (L.) L.	Jamaica	Leaves, Flowers, Stem	Jamaicolide A	*C96*	Ober et al. (1985d)
			Jamaicolide B	*C97*	
			Jamaicolide C	*C98*	
			Jamaicolide D	*C99*	
Calea lantanoides Gardner	Brazil	Aerial parts	15-Deoxybudlein A	*C100*	Vichnewski et al. (1982)
Calea leptocephala S.F. Blake	Mexico	Leaves, Flowers, Stem	8β-Angeloyloxy-9α-acetoxycalyculatolide	*C101*	Ober et al. (1986)
			Desacetylcalein A	*C102*	
			8β-Angeloyloxyleptocephalide	*C103*	
Calea megacephala B.L. Rob. & Greenm.	Mexico	Leaves, Flowers, Stem	Desacylisovalerylheliangine	*C104*	Ober et al. (1987b)
			8β-Methacryloyloxytemifolin	*C105*	

Table 1. Cont'd.

Calea morii H. Rob.	Brazil	Air-dried plant material	2,3-Dimethyl-6-(acetoxy acetyl)-7-methoxy chromene	*C106*	Bohlmann et al. (1981a)
			11,13-Dihydro-11,13-epoxyatripliciolide angelate	*C107*	
			11,13-Dihydro-11,13-epoxyatripliciolide tiglate	*C108*	
			11-Hydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-angelate	*C109*	
			11-Hydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-tiglate	*C110*	
			3β-Acetoxy-8β-angeloyloxy-1,10-dihydro-1α,10β-epoxycostunolide	*C111*	
			5-Myrtenyl-4,5-11,13-tetrahydro-11,13-epoxyatripliciolide-8-O-angelate	*C112*	
Calea nelsonii B.L. Rob. & Greenm.	México	Aerial parts	10-acetoxy-8,9-epoxy-7-isobutyryloxythymol isobutyrate	*C113*	Martinez et al. (1987a)
			10-acetoxy-8,9-epoxy-7-hydroxythymol isobutyrate	*C114*	
			8-Hydroxy-9-acetoxy-loisobutyryloxythymol	*C115*	
			7-Acetoxy-8-hydroxy-9,l0-diisobutyryloxythymol	*C116*	
			7-Isobutyryloxy-8,9dihydroxythymol	*C117*	
			8,9-epoxy-7-isobutyryloxythymol isobutyrate	*C118*	
Calea oxylepis Baker	Brazil	Air-dried plant material	1β-Hydroxy-8-desacylzacatechinolide-(2-methylbutyrate)	*C119*	Bohlmann et al. (1982a)
			1α-Acetoxy-8-desacylzacatechinolide-(2-methylbutyrate)	*C120*	
			1-Oxo-8-desacetylzacatechinolide-(2-methylbutyrate)	*C121*	
			1 ,2-Diacetoxy-1,2-dihydroartemisia alcohol acetate	*C122*	
Calea peckii B.L. Rob.	Costa Rica	Leaves, Flowers	4,6-Dimethoxy-2-isopropylidene-3oxo-2,3-dihydrobenzofurane	*C123*	Castro et al. (1989)
			1β-Hydroxy-Bisabola-2,10-dien-4-one	*C124*	
			1α-Hydroxy-Bisabola-2,10-dien-4-one	*C125*	
			4-Hydroxy-3methoxybisabola-1,10-diene	*C126*	
			1α-Hydroxy-8β-tigloyloxyguaia-3,9,11(13)-trien-1,2,6α-olide	*C127*	
			3β-Hydroxy-8β-tigloyloxyheliangolide	*C128*	
Calea pilosa Baker	Brazil	Air-dried plant material	2-[2-Acetoxyethyl]-5-prop-1-inyl-dithienyl	*C129*	Bohlmann et al. (1981a)
			Atripliciolide angelate	*C130*	
			9α-Hydroxyatripliciolide-8-O-angelate	*C131*	
			9α-Hydroxyatripliciolide-8-O-tiglate	*C132*	
			11,13-Dihydro-11,13-epoxyatripliciolide angelate	*C107*	
			11,13-Dihydro-11,13-epoxyatripliciolide tiglate	*C108*	
			11,13-Dihydro-11,13-epoxyatripliciolide methacrylate	*C133*	
			9α-Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-angelate	*C134*	
			9α-Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-tiglate	*C135*	
			9α-Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-methycrylate	*C136*	
			11-Hydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-angelate	*C109*	
			9α,11-Dihydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-angelate	*C137*	
			3β-Acetoxy-8β-angeloyloxy-1,10-dihydro-1α,10β-epoxycostunolide	*C111*	
			5-Myrtenyl-4,5-11,13-tetrahydro-11,13-epoxyatripliciolide-8-O-angelate	*C112*	

Table 1. Cont'd.

	Brazil	Aerial parts	4-Glycosyloxybenzoic acid Anisic acid Tetradeca-4E,6E,12E-trien-8,10-diyn-1-ol Arucanolide	*C138* *C139* *C140* *C141*	Ferreira et a. (1980)
Calea pinnatifida (R. Br.) Less.	Brazil	Leaves	6-Acetyl-7-hydroxy-2,2-dimethylchromene 6-Acetyl-7-methoxy-2,2-dimethylchromene 6-(1-Hydroxyethyl)-7-methoxy-2,2-dimethylchromene 6-(1-Ethoxy)-7-methoxy-2,2-dimethylchromene	*C142* *C143* *C144* *C145*	Lima et al. (2015a)
	Brazil	Leaves	Ethyl caffeate Vanilin 12-hydroxy-encecalin Phytol 3,4-di-O-caffeoylquinic acid 3,5-di-O-caffeoylquinic acid 4,5-di-O-caffeoylquinic acid 11,13-dihydroxy-calaxin	*C146* *C147* *C148* *C149* *C150* *C151* *C152* *C153*	Lima et al. (2016)
Calea platylepis Sch. Bip. ex Baker	Brazil	Leaves, Flowers, Underground parts	Genkwanin (+)-4□,7□-Aromadendranediol Euparin Caleprunin A Caleprunin B Euparone	*C154* *C155* *C156* *C157* *C158* *C159*	Nascimento et al. (2004a)
Calea prunifolia Kunth	Panama		Acacetin Calbertolide C Prunichromene A Prunichromene B	*C3* *C4* *C160* *C161*	Ober et al. (1985b)
	Costa Rica	Leaves, Flowers	Caleprunin A Caleprunin B	*C157* *C158*	Ober et al. (1985e)
	Costa Rica	Leaves, Flowers	4,6-Dimethoxy-2-isopropylidene-3oxo-2,3-dihydrobenzofurane 7-Methoxycaleteurcrin Caleprunifolin 2-Senecioyl-hydroxyquinone-4-O-methyl ether 5α-Hydroperoxy-costol acetate	*C123* *C162* *C163* *C164* *C165*	Castro et al. (1989)
	Colombia	Leaves	1-(2-Hydroxy-5-(1-methoxyethyl)phenyl)-3-methylbut-2en-1-one	*C166*	Gomez and Gil (2011)

Table 1. Cont'd.

			1-(2-Hydroxy-5-methoxyphenyl)-3-methylbut-2-en-1-one	*C167*	
	Colombia	Leaves	Quercetin 3-rutinoside 3,5-Di-*O*-[E]-caffeoylquinic acid ent-15b-(β-D-Glucopyranosyloxy)-kaur-16-en-19-oic acid β-D-glucopyranosyl ester	*C168* *C169* *C170*	Puebla et al. (2011)
Calea reticulata Gardner	Brazil	Air-dried plant material	Germacra-4(15), 5, 10(14)-trien-1-one 6-Epi-β-verbesinol coumarate	*C171* *C172*	Bohlmann et al. (1982b)
Calea rotundifolia (Less.) Baker	Brazil	Air-dried plant material	1β,10α-Epoxy-8β-tiglinoyloxy-1,10-dihydrocostunolide Heliangin-3-*O*-acetate 8β-Tiglinoyloxyreynosin Iβ-Hydroxy-8β-tiglinoyloxyarbusculin B 8β-Tiglinoyloxybalchanin 3-Hydroxy-octa-1,5t-dien-7-one	*C173* *C174* *C175* *C176* *C177* *C178*	Bohlmann et al. (1981b)
Calea rupícola Chodat	Paraguay	Leaves, flowers, Stem, roots	9α-Hydroxyatripliciolide-8-*O*-isobutyrate 5β-Myrtenyl-4α,5-dihydroatripliciolide-8-*O*-isovalerate	*C179* *C180*	Schmeda-Hirschmann et al. (1986)
	Brazil	Aerial parts	Eupatoriochromene Precocene II	*C181* *C182*	Steinbeck et al. (1997)
Calea serrata Less.	Brazil	Leaves Stems	Precocene II Sesquiterpene hydrocarbons germacrene D β-Selinene Bicyclogermacrene	*C182* *C183* *C62* *C184*	Ribeiro et al. (2011)
Calea solidaginea Kunth	Venezuela	*NR	Acacetin Heliangine Calbertolide C 8-Epi-8-tiglylrupicolin A Desacyl-8-tiglylsubcordatolide A	*C3* *C185* *C4* *C6* *C5*	Ober et al. (1985c)
	Venezuela	Leaves, flowers, stem, roots	Solidaginolide A Solidaginolide B	*C186* *C187*	Ober et al (1985c)
	Venezuela	Air-dried plant material	8-Epi-isobutyrylrupicolin A 8-Epi-isobutyrylrupicolin B	*C188* *C189*	Ober et al. (1984c)
	Venezuela	Air-dried plant material	Subcordatolide A Subcordatolide B	*C190* *C191*	Ober et al. (1984d)

Table 1. Cont'd.

	Venezuela	Leaves, Flowers, Stem, Roots	Subcordatolide C	*C192*	Ober et al. (1984e)
	Venezuela	Leaves, flowers, stem, roots	Subcordatolide D Subcordatolide E	*C193* *C194*	Ober et al. (1987a)
	Mexico	Dried leaves	9α-Acetoxyzexbrevin 9α-Hydroxy-11,13-dihydro-11α,13-epoxyatripliciolide-8β-*O*[2-methylacrylate] 9α-Hydroxy-11,13-dihydro-atripliciolide-8β-O-[2-methylacrylate]	*C195* *C196* *C197*	Lee et al. (1982b)
Calea ternifolia var. calyculata (B.L. Rob.) Wussow, Urbatsch & G.A. Sullivan	Mexico	Dried leaves	8β-Angeloyloxy-9α-acetoxyternifolin 8β-Angeloyloxy-9α-[2-methylbutanoyloxy]-ternifolin	*C198* *C199*	Lee et al. (1982a)
	Mexico	Dried aerial parts	8β-Angeloyloxy-9α-hydroxycalyculatolide 8β-Methylacryloyloxy-9α-hydroxycalyculatolide 15-Hydroxy-11,13-dihydro-11α, 13-epoxyatripliciolide-8β-O-angelate	*C200* *C201* *C202*	Fischer et al. (1984)
Calea teucrifolia (Gardner) Baker	Brazil	Aerial parts	5-Hydroxynerolidol 5-Acetoxynerolidol	*C203* *C204*	Bohlmann et al. (1981c)
	Mexico	Air-dried plant material	Trichomatolide A	*C205*	Ober et al. (1984a)
Calea trichomata	Mexico	Air-dried plant material	3-Deoxy-2,3-dehydroheliangin Trichomatolide B Trichomatolide C Trichomatolide D Trichomatolide E	*C206* *C207* *C208* *C209* *C210*	Ober et al. (1984b)
	Brazil	Steam,Roots	2-Senecioyl-4-(hydroxyethyl)-phenol 2-Senecioyl-4-(angeloyloxyethyl)-phenol 2-senecioyl-4-(methoxyethyl)-phenol 2-senecioyl-4-(pentadecanoyloxyethyl)-phenol	*C211* *C212* *C213* *C214*	Nascimento et al. (2004b)
Calea uniflora Less.	Brazil	Underground parts	Uniflorol-A Uniflorol-B 2,2-Dimethyl-6-(1-hydroxyethyl)-chroman-4-one	*C215* *C216* *C15*	Nascimento et al. (2007a)
	Brazil	Leaves	Neurogenin Ethyl caffeate Butein Orobol	*C217* *C146* *C218* *C219*	Lima et al. (2015b)

Table 1. Cont'd.

			α-Hydroxy-butein	*C220*	
			Caffeic acid	*C221*	
			Butein 4'-*O*-glucopyranosyl	*C222*	
			Quercetin 3-*O*-glucopyranosyl	*C223*	
			3,5-di-O-caffeoylquinic acid	*C151*	
	*NR	Seed oil	trans-3,cis-9,cis-12-octadecatrienoic acid	*C224*	Bagby et al. (1965)
	*NR	Leaves	6-Methoxy-isoeugenol-isobutyrate	*C225*	Bohlmann and Jakupovic (1979)
			Caleurticin	*C226*	
			9α-Hydroxy-atripliciolid-8-O-[2-methylacrylate]	*C227*	
			9α-[Isovaleryloxy-bzm. Senecioyloxy-bzw. Angeloyloxy]-15-hydroxy-atripliciolid-8-O-[2-methylacrylate]	*C228*	
			Caleurticolidacetate	*C229*	
			Caleurticolide-[2-methylacrylate]	*C230*	
			Caleurticolide-angelicate	*C231*	
Calea urticifolia DC.	El Salvador	Dried leaves	Juanislamin	*C232*	Castillo et al. (1981)
			2,3-epoxy-juanislamin	*C233*	Ohguchi et al. (2009)
	Mexico	Leaves	Calealactone A	*C234*	Yamada et al. (2004) Ohguchi et al. (2009)
			Calealactone B	*C235*	
			Calealactone C	*C236*	
			2,3-epoxy-calealactone A	*C237*	
			Calein D	*C238*	
			Juanislamin	*C232*	
			2,3-epoxy-juanislamin	*C233*	
		Leaves	Arucanolide	*C141*	Ohguchi et al. (2009)
Calea villosa Baker	Brazil	Air-dried plant material	8β-Angeloxyloxy-3β-(2-methylbutyryloxy)-1β,10α-epoxy-1,10H-costunolide	*C239*	Bohlmann et al. (1982e)
			11,13-Epoxy-11,13H-budlein A	*C240*	
			11β-Hydroxy-13-chloro-11,13H-budlein A	*C241*	
Calea zacatechichi Schltdl.	*NR	Aerial parts	1α-Acetoxy-zacatechinolide	*C242*	Bohlmann and Zdero (1977b)
			1-Oxo-zacatechinolide	*C243*	
	*NR	*NR	Calein A	*C244*	Quijano et al. (1979)
			Calein B	*C245*	
	Mexico	Leaves, Flowers	Zexbrevin	*C246*	Herz and Kumar (1980)
		Aerial parts	Calein E	*C247*	Martinez et al. (1987b)

Table 1. Cont'd.

		Calein F	*C248*	
		4',5-Dihydroxy-7-methoxyflavone	*C249*	
		5,7-Dihydroxy-3',4'-dimethoxyflavone	*C250*	
	Air dried leaves	4',5,7-Trihydroxyflavone	*C251*	Kohler et al. (2002)
		5-Hydroxy-3',4',7-trimethoxyflavone	*C252*	
		5-Hydroxy-4',7-dimethoxyflavone	*C253*	
		Calein A	*C244*	
		Calein D	*C238*	
		Calealactone C	*C236*	
*NR	Leaves,Stems	Calealactone D	*C254*	Wu et al. (2011)
		Calealactone E	*C255*	
		8β-angeloxy-9α-acetyloxycalyculatolide	*C256*	

*NR: Not reported.

rather than an α-methylene-γ-lactone. Finally, they could have useful antihypertensive properties through increasing NO levels, resulting in vascular relaxation of the smooth muscle (Seca et al., 2015).

Diverse biological activities have been attributed to the genus *Calea*. Notably however, several studies solely reported isolation of phytochemicals without parallel biological testing, revealing a gap in current knowledge. Known biological activities are discussed in the following paragraphs.

Antiplasmodial effects

Leaves from *C. zacatechichi* showed antiplasmodial activity in an investigation of medicinal plants from El Salvador. In this study, it was assumed that isolated flavones represented the major antiprotozoal principles. For investigation of *C. zacatechichi*, air dried leaves (300 g) were extracted with petrol-EtOAc (1:1 V/V) and MeOH. The extract was subjected to column chromatography and sequentially eluted with MeOH-H_2O mixtures of decreasing polarity. Five flavones were identified: 4',5-Dihydroxy-7-methoxyflavone (C249), 5,7-Dihydroxy-3',4'-dimethoxyflavone (C250), 4',5,7-Trihydroxyflavone (C251), 5-Hydroxy-3',4',7-trimethoxyflavone (C252), 5-Hydroxy-4',7-dimethoxyflavone (C253) (Table 1 and Figure 1). The isolated flavones were identified by H-NMR and MS. The lipophilic crude extract showed significant antiplasmodial activity *in vitro* with IC_{50} values between 6 and 25 µg/ml. All flavones isolated from *C. zacatechichi* had activity against *Plasmodium falciparum*, with IC_{50} values ranging from 4 to 40 µM (Köhler et al., 2002).

Leishmanicidal effects

Various studies have investigated leishmanicidal activity of the genus *Calea*. A study performed with leaves of *Calea pinnatifida* demonstrated leishmanicidal activity. Fresh leaves of *C. pinnatifida* (800 g) were extracted by maceration for 15 days at room temperature with ethanol 92%. After evaporation of the solvent, 12 g of ethanolic extract was obtained. Sub-fractions were then obtained, using solvents of increasing polarity. The hexane fraction was purified by column chromatography on silica gel and preparative thin layer chromatography (TLC) to afford four chromones: 6-Acetyl-7-hydroxy-2,2-dimethylchromene (C142), 6-Acetyl-7-methoxy-2,2-dimethylchromene (C143), 6-(1-Hydroxyethyl)-7-methoxy-2,2-dimethylchromene (C144) and 6-(1-Ethoxy)-7-methoxy-2,2-dimethylchromene (C145) (Table 1), but only two compounds (C143 and C144) exhibited moderate activity (Figure 2). Structure identification of isolated compounds involved analysis of spectral data of 1D and 2D-NMR. To evaluate antileishmanial activity, a culture of human cells and *Leishmania amazonensis* was utilized (Lima

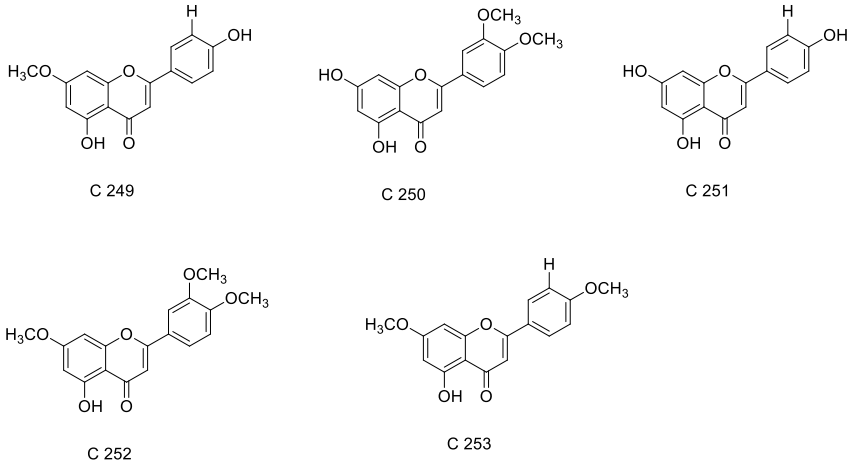

Figure 1. Flavonoids isolated from *Calea zacatechichi* with antiplasmodial activity.

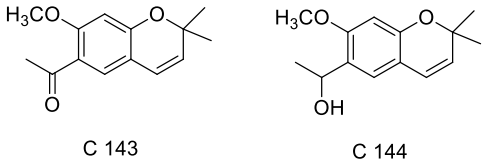

Figure 2. Chromenes of *Calea pinnatifida* with *in vitro* leishmanicidal activity.

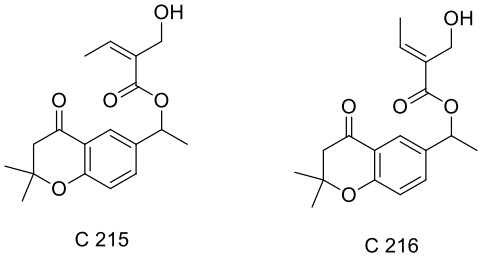

Figure 3. Chromanones isolated from *Calea uniflora* with leishmanicidal activity.

et al., 2015a).

A study on dichloromethane and ethyl acetate fractions of the leaves of C. uniflora did not exhibit promising leishmanicidal activity, but instead displayed trypanocidal activity. Nine phenolic compounds were identified, namely neurogenin (C217), ethyl caffeate (C146), butein (C218), orobol (C219), α-hydroxy-butein (C220), caffeic acid (C221), butein 4'*O*-glucopyranosyl (C222), quercetin 3-O-glucopyranosyl (C223) and 3,5-di-*O*-caffeoylquinic acid (C151) (Table 1) (Lima et al., 2015b).

In contrast, another study showed that a mixture of two chromanones uniflorol-A (C215) and uniflorol-B (C216) (Table 1) from underground organs of *C. uniflora* had leishmanicidal activity. Dried and powdered underground parts of *C*. *uniflora* (200 g) were exhaustively extracted with dichloromethane at room temperature and 4.2 g of crude extract was obtained. Various chromatographies were performed, including TLC and HPLC, and NMR was used to deduce the structures. The inseparable mixture of uniflorol-A and uniflorol-B significantly inhibited *Leishmania major* promastigote growth *in vitro* by 54.8, 81.5 and 88.9% at concentrations of 25, 50 and 100 µg/ml, respectively (Nascimento et al., 2007a) (Figure 3).

Germacranolides of *C. zacatechichi* were evaluated and also showed leishmanicidal activity. Six compounds were isolated and identified as calealactone C (C236), calein D (C238), calein A (C244), calealactone E (C255), 8β-angeloxy-9α-acetyloxycalyculatolide (C256) and a new compound calealactone D (C254) (Figure 4). All the compounds possessed leishmanicidal effects compared with the positive control pentamidine. The crude methanol extract obtained by percolation was sequentially extracted with chloroform and hexane and subjected to vacuum liquid chromatography on silica gel, eluting successively with gradient n-hexane-ethyl acetate mixtures of increasing polarities (Wu et al., 2011).

Trypanocidal effects

C. uniflora extracts have also been evaluated for trypanocidal and fungicidal activities. Extracts exhibited high trypanocidal activity, lysing 99% of parasites. However, the extracts were not as effective against fungi, showing fungicidal activity *in vitro* against just two dermatophytes. Four *p*-hydroxyacetophenone derivatives were isolated from the extracts: 2-Senecioyl-4-(hydroxyethyl)-phenol (C211), 2-Senecioyl-4-(angeloyloxyethyl)-phenol (C212), 2-senecioyl-4-(methoxyethyl)-phenol (C213) and 2-senecioyl-4-(pentadecanoyloxyethyl)-phenol (C214) (Table 1 and

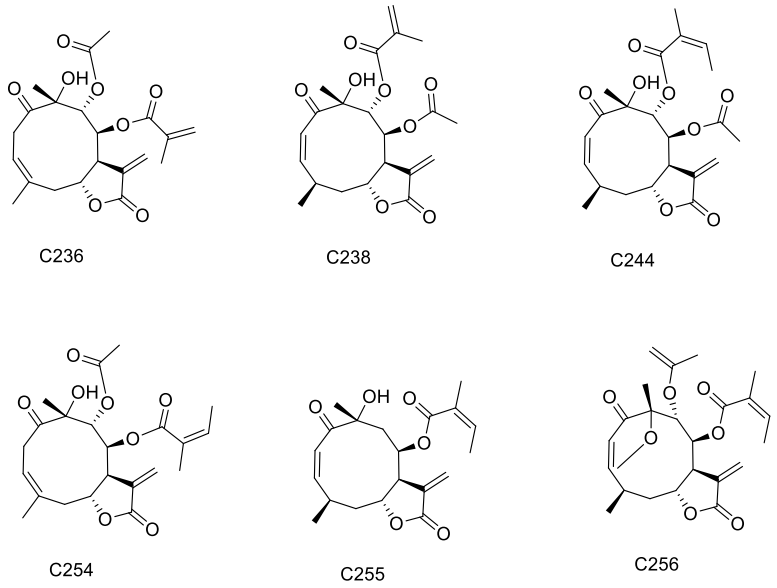

Figure 4. Sesquiterpene lactones isolated from *Calea zacatechichi* with leishmanicidal activity.

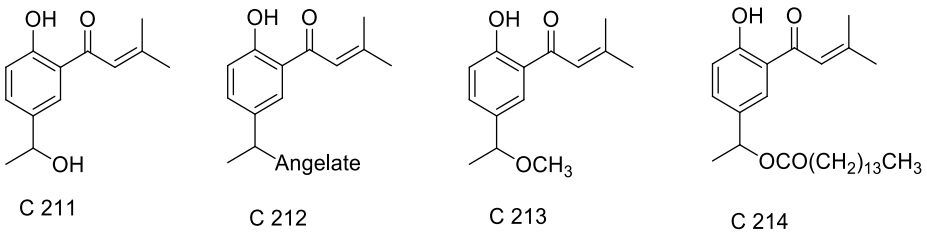

Figure 5. *p*-hydroxyacetophenone derivatives from *Calea uniflora* with trypanocidal properties.

Figure 5). These compounds were isolated from the dichloromethane fraction and identified by NMR. Only compounds C211 and C214 (Figure 5) showed trypanocidal activity in vitro, lysing 70 and 71% of parasites at 500 µg/ml (Nascimento et al., 2004a). Other phenolic compounds of *C. uniflora* have exhibited trypanocidal activity. Fresh leaves were extracted by maceration at room temperature with ethanol 92% for 15 days. Further fractions were obtained through selective partitioning (with hexane, dichloromethane and ethyl acetate). Chromatographic (vacuum liquid chromatography and gel column) separations afforded several compounds. Those showing trypanocidal activity *in vitro* were ethyl caffeate (C146) and a mixture of butein (C218) + orobol (C219), displaying IC_{50} values of 18.27 and 26.53 µM, respectively (Lima et al., 2017) (Figure 6).

Two flavonoids obtained from ethanolic extract of aerial parts of *Calea clausseniana* were evaluated for their *in vitro* trypanocidal activity against the trypomastigote forms of *Trypanosoma cruzi*, with neither compound showing trypanocidal activity (Nascimento and Oliveira, 2007b).

Acaricidal activity

One study was performed to evaluate the acaricidal properties of the essential oil obtained from *C. serrata*. This study demonstrated that both the essential oil and the isolated precocene II were toxic to the larvae of the tick *Rhipicephalus microplus.* The essential oil was obtained from fresh leaves of the plant by hydrodistillation using a Clevenger-type apparatus. The oil was analyzed by gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS). For extraction and isolation of precocene II, air-dried and powdered plant material was extracted by repeated maceration with n-hexane. Precocene II (C182) (Table 1 and Figure 7) was isolated from this extract by column chromatography using silica gel 60 and *n*-hexane:

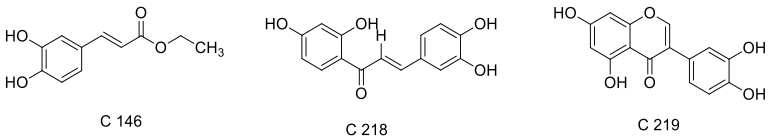

Figure 6. Phenolic compounds of *Calea uniflora* with trypanocidal activity.

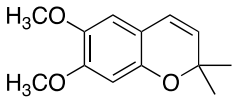

Figure 7. Chromene (Precocene II) isolated from *Calea serrata* with acaricidal activity.

dichloromethane, in increasing polarities, obtaining some fractions rich in precocene II (Ribeiro et al., 2011). Precocene II (C182) had been previously reported in the literature (Steinbeck et al., 1997).

Vasodilator activity

Chemical investigation of the leaves of *Calea prunifolia* has resulted in the isolation of three compounds: Quercetin 3-rutinoside (C168), 3,5-Di-*O*-[E]-caffeoylquinic acid (C169) and ent-15b-(β-D-Glucopyranosyloxy)-kaur-16-en-19-oic acid β-D-glucopyranosyl ester (C170) (Table 1 and Figure 8). Their chemical structures were elucidated on the basis of spectral analysis, including HRMS, 1D- and 2D-NMR. The vasodilator effect related to anti adrenergic activity of the three compounds was evaluated in isolated aortic rings from *Wistar* rats contracted cumulatively with phenylephrine (from 1×10^{-9} to 5×10^{-5} mol L^{-1}). Although these compounds were devoid of significant vasodilator activity when they were tested alone (1 µg mL^{-1}), both mixtures (1:1:1) and the EtOH extract exerted preventive anti-adrenergic activity increasing the phenylephrine CE_{50} from 2.3×10^{-8} to 1.3×10^{-7} and 8.0×10^{-7} mol/L^{-1}, respectively. While a mixture of these three compounds exerted preventive anti-adrenergic activity, they did not show vasodilator activity (Puebla et al., 2011).

Anti-inflammatory effects

A study of *C. prunifolia* revealed two chemical compounds, one of which showed topical anti-inflammatory activity. Both compounds were derived from *p*-hydroxyacetophenone. The compound that presented satisfactory anti-inflammatory activity was 1-(2-hydroxy-5-(1-methoxyethyl)phenyl)-3-methybut-2-en-1-one (C166) (Table 1 and Figure 9). Dried leaves of *C. prunifolia* were extracted by percolation with ethanol at room temperature and the extract was concentrated under vacuum at 35°C. The crude extract was chromatographed on a silica gel column with CH_2Cl_2 obtaining five fractions. In the experiment, edema was induced in the ears of female mice by the topical application of 2.5 µg TPA to the ear surfaces. Subsequently, the right ear received the extracts at a concentration of 500 µg per ear, using indomethacin as reference substance in all cases. Although one of the compounds had anti-inflammatory activity, it was suggested that synthetic modification would be necessary to increase the anti-inflammatory activity of these compounds (Gómez and Gil, 2011).

The aqueous extract of *C. zacatechichi* showed potential antiiflammatory activity preventing the formation of edema after administration of carrageenan. Powdered leaves (1 g) were extracted with distilled water, heating for 10 min at 95°C. Following centrifugation at 100 g, the supernatant was adjusted to pH 7.4. For the biological assay, male *Wistar* rats (200 to 250 g) and Swiss albino mice (20 to 25 g) were used. The extracts were administered and compared with both indomethacin and a negative control. In this study, only crude extracts were evaluated for anti-inflammatory activity and no individual compounds were isolated. The study concluded that *C. zacatechichi* contains compounds with potential anti-inflammatory activity and that this activity can be associated with the biosynthesis of prostaglandins and lipoxygenase products (Venegas-Flores et al., 2002). Other studies of *C. zacatechichi* have revealed the presence of sesquiterpene lactones (Herz and Kumar, 1980) and chromenes (Quijano et al., 1977) and these compounds are known to be associated with anti-

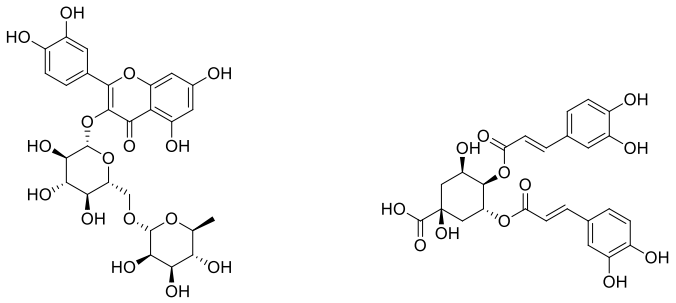

Figure 8. Phenolic compounds from *Calea prunifolia* with vasodilator activity.

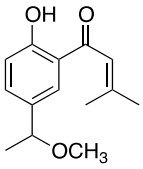

Figure 9. *p*-hydroxyacetophenone derivative isolated from *Calea prunifolia* with anti-inflammatory activity.

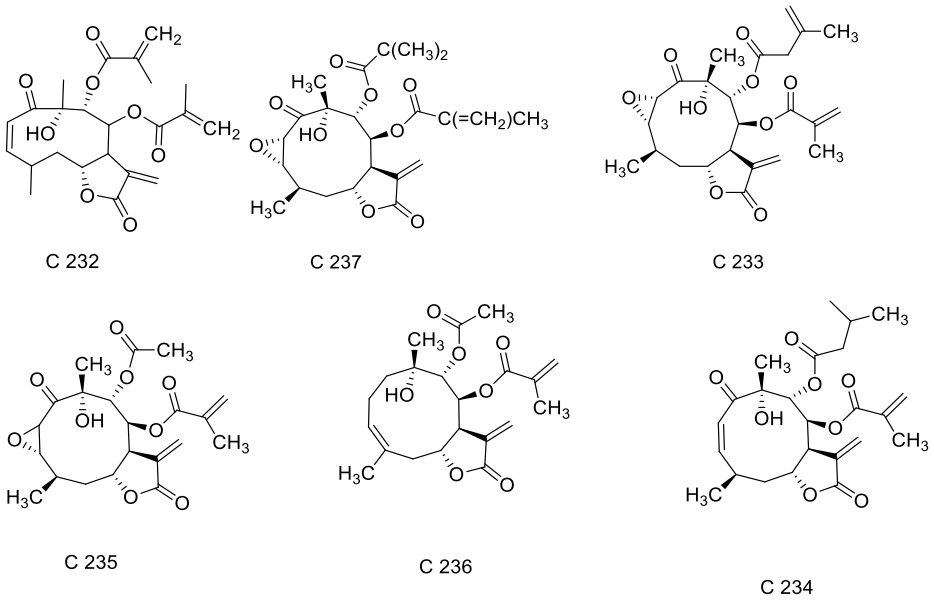

Figure 10. Sesquiterpene lactones from *Calea urticifolia* tested for cytotoxic activity.

inflammatory activity.

Cytotoxic effects

Cytotoxic activity was observed in a study of *C. urticifolia*. The major sesquiterpene lactones isolated from the acetone extract exhibited anti-melanotic activity in mouse B16 melanoma cells. The results suggested that the inhibitory effects of sesquiterpene lactones on melanin biosynthesis may be due to the suppression of tyrosinase expression. In particular, 2,3-epoxy-juanislamin (C233) (Table 1 and Figure 10) was notable for its potentinhibitory activity on melanogenesis through

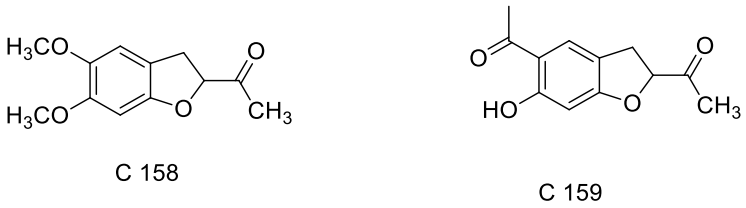

Figure 11. Benzofurans isolated from *Calea platylepis* with antimicrobial activity.

modulating the transcriptional machinery of tyrosinase mRNA (Ohguchi et al., 2009).

In another study, the anticancer activity of the dichloromethane crude extract obtained from *C. pinnatifida* was evaluated. Dried aerial parts of*C. pinnatifida* were ground and an aliquot extracted by soxhlet with dichloromethane (DCE). The DCE showed high potency and selectivity for melanona and kidney cell lines. An *in vivo* study using Erlich ascites tumor and Erlich solid tumor further validated the cytotoxic effects of DCE. The substance(s) involved in the antitumor effect of *C. pinnatifida* DCE are unknown, although some compounds known from the extract, such as the sesquiterpene lactones, could explain these results (Marchetti et al., 2012).

Antimicrobial activity

Extracts of leaves and flowers of *Calea platylepis* have shown antimicrobial activity against bacteria and fungi. These activities were performed by the well diffusion method, evaluating compounds in the range of 50 to 1000 µg/ml. Bacitracin and ketoconazole were used as positive controls for bacterial and fungal strains, respectively. Certain compounds, namely (+)-4α,7β-Aromadendranediol (C155), euparin (C156), caleprunin B (C158) and euparone (C159) (Table 1 and Figure 11), demonstrated a broad spectrum of action, inhibiting the growth of various strains of microorganisms (bacteria and fungi).

The flavonoid genkwanin (C154) was inactive against all the microorganisms, while caleprunin A (C157) showed antifungal activity against the dermatophyte *Trichophyton mentagrophytes* (Nascimento et al., 2004b). Several compounds have been isolated in other studies of *C. platylepis*, including sesquiterpenes, flavonoids, benzofurans, steroid saponins and *p*-hydroxyacetophenone derivatives (Nascimento et al., 2002).

The essential oil of *Calea fruticosa* showed antimicrobial activity against Gram-negative bacteria (*Proteus vulgaris*), although activity proved to be selective as there was no activity against yeast strains. This study involved hydrodistillation of the leaves, GC/MS analysis of the essential oil and subsequent evaluation of the essential oil against a panel of microorganisms. *C. fruticosa* essential oil was characterized by 43 constituents, representing 62.9% of the total oil composition. The essential oil was dominated by the presence of oxygenated sesquiterpenes and sesquiterpene hydrocarbons, with caryophyllene (C69), α-cadinol (C76) and sellin-11-en-4-α-ol (C77) (Table 1) as the most abundant components (Carvalho et al., 2014). The antibacterial activity of the oil was ascribed to the synergistic effects of α-pinene and linalool (Sivasothy et al., 2011).

Antifungal activity of *Calea clematidea* was shown to be moderate against *Trichophyton tonsurans, Trichophyton rubrum, Trichophyton menthagrophytes var. interdigitale, Epidermophyton floccosum, Microsporum gypseum, Microsporum canis* and *Microsporum nanum.* The essential oils described were shown to inhibit fungal growth. Fresh leaves and flowers were subjected to steam distillation for 4 h using a Clevenger-type apparatus, followed by exhaustive extraction of the steam distillate with diethyl ether. The antifungal activities against pathogenic fungi, from patient isolates, were determined using the dilution technique. The minimum inhibitory concentration (MIC) was measured for the leaf essential oil and clemateol, and both showed moderate fungistatic and fungicidal action against dermatophytes (Flach et al., 2002).

Antidiarrheal and antinociceptive effects

Calea zacatechichi extracts exhibited antidiarrheal and antinociceptive effects in mouse models of irritable bowel syndrome. A methanolic macerate was further extracted with dichloromethane (DCM) to yield a solid extract. According to this paper, such extracts may be used as a source material to treat pain and diarrhea associated with irritable bowel syndrome (Salaga et al., 2015).

C. uniflora Less. was investigated for antinociceptive effects and cytotoxicity. Regarding antinociceptive activity, models produced significant results at doses corresponding to 100 and 300 mg/kg of the crude extract compared to the control. The rota rod model was favoured since the extract did not cause motor

incoordination and sedation in the experiment. In the *in vitro* cytotoxic tests, both crude extracts and ethyl acetate and butanolic fractions produced IC_{50} values greater than 58 µg/ml with the HaCaT lineage and 48 µg/ml with the B16-F1 lineage; thus, these values did not indicate cytotoxic effects. Phytochemical analyses verified the presence of flavonoids and sesquiterpenes within *C. uniflora* extracts (Torres et al., 2016).

Anti-obesity effects

A study of *C. urticifolia* indicated the possibility that germacranolides obtained from acetone extract of the leaves of this species have anti-obesity effects. The germacranolides inhibited preadipocyte differentiation in 3T3-L1 cells, suggesting this activity. Inhibition of the differentiation of 3T3-L1 cells to adipocytes is beneficial for the prevention of obesity complicated by atherosclerosis (Matsuura et al., 2005).

Conclusion

The genus *Calea* contains several potential pharmacophores for drug discovery programmes, notably chromenes as anti-inflammatory and anticancer agents but also for their diverse sesquiterpene lactone consituents.

However, prior to the application or recommendation of these species to prevent or treat disease states, additional pharmacological and toxicological studies are essential; notably, no literature reports exist on the safety and efficacy of the 37 species described in this paper.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

ACKNOWLEDGEMENTS

The authors are thankful to the National Council for Scientific and Technological Development (CNPq) and Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES – Edital PVE nº 09/2014) for funding and scholarships.

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