

Review

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

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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 exocyclic 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- κ B 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- κ B 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				
<i>Calea angusta</i> S.F.Blake	Brazil	Air-dried plant material	11,13-Dihydro-11,13-epoxyatripliciolide-2-methylbutyrate	C1	Bohlmann et al. (1982d)				
			9 α -Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-2-methylbutyrate	C2					
<i>Calea berteriana</i> DC.	Colombia	Air-dried plant material	Acacetin	C3	Ober et al. (1985b)				
			Calbertolide C	C4					
			Desacyl-8-tiglysubcordatolide A	C5					
	Venezuela	Dried leaves	8-Epi-8-tiglylrupicolin A	C6					
			8-Epi-8-tiglylrupicolin B	C7					
<i>Calea clauseniana</i> Baker	Brazil	Underground parts	Calebertin	C8	Nascimento and Oliveira (2007b)				
			Calbertolide A	C9					
			Calbertolide B	C10					
			Aerial parts	7-O-(β -L-Rhamnopyranosyl-(1-2)- β -D-glucopyranosyl)-30,40,7-trihydroxyflavone		C11			
			Uniflorol A acetate	C12					
<i>Calea clematidea</i> Baker	Paraguay	Leaves, Flowers	Uniflorol B acetate	C13	Flach et al. (2002)				
			2,2-dimethyl-6-[[4'-acetoxy]angeloyloxy]ethyl]chroman-4-one	C14					
			2,2-Dimethyl-6-(1-hydroxyethyl)-chroman-4-one	C15					
			2-Senecioid-4-[1-(angeloyloxy)ethyl]phenol	C16					
			2-Senecioid-4-[1-(acetylsarracinoyloxy)-ethyl]phenol	C17					
			Clemateol	C18					
			<i>o</i> -Vanillin	C19					
<i>Calea crocinervosa</i> Wussow, Urbatsch & G.A.Sullivan	Mexico	Aerial parts	Spathulenol	C20	Ortega et al. (1989)				
			α -Terpinene	C21					
			Germacrene	C22					
			Yomogi alcohol	C23					
			β -Caryophyllene	C24					
			<i>m</i> -Cymene	C25					
			<i>o</i> -Cymene	C26					
			α -Gurjunene	C27					
			<i>Calea cuneifolia</i> DC.	Brazil		Air dried xylopodium	Crocinevolid	C28	Lourenço et al. (1981)
							1,1'-Bis-[2-senecionyl-4-(1-ethyl)-phenoxy]ether	C29	
Meso-1,1'-Bis-[2-senecionyl-4-(1-ethyl)-phenoxy]ether	C30								
			2-Senecionyl-4-vinylphenol	C31					

Table 1. Cont'd.

			2-Senecionyl-4-(1-hydroxyethyl)-phenol	C32	
			2-Senecionyl-4-(1-acetoxyethyl)-phenol	C33	
			2-Senecionyl-4-(1-acetylsarracinyloxyethyl)-phenol	C34	
			2-(3-Methyl-3-hydroxybutanoyl-1)-4-(1-hydroxyethyl)-phenol	C35	
			6-Hydroxy-2,2-dimethylchroman-4-one	C36	
			Acetylsarracinic acid	C37	
			α -Pinene	C38	
			<i>p</i> -Cymene	C39	
			Limonene	C40	
			Lavender lactone	C41	
			<i>cis</i> -Arbusculone	C42	
			<i>trans</i> -Arbusculone	C43	
			Linalool	C44	
			<i>cis</i> -Linalool oxide	C45	
			<i>trans</i> -Linalool oxide	C46	
			Terpinen-4-ol	C47	
			<i>p</i> -Cymen-8-ol	C48	
			<i>trans</i> -Carveol	C49	
			Carvone	C50	
			β -Elemene	C51	
			Cyclosativene	C52	
			α -Copaene	C53	
			β -Bourbonene	C54	
			β -Cubebene	C55	
			β -Elemene	C56	
			(<i>E</i>)-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	
			β -Cadinene	C65	
			Cubebol	C66	
			<i>trans</i> -Calamenene	C67	
			(<i>E</i>)-Nerolidol	C68	
			Spathulenol	C20	
			Caryophyllene oxide	C69	
			Gleenol	C70	
<i>Calea fruticosa</i> (Gardner) Urbatsch, Zlotzky & Pruski.	Brazil	Leaves			Carvalho et al. (2014)

Table 1. Cont'd.

			Globulol	C71	
			Humulene epoxide II	C72	
			Junenol	C73	
			1-epi-Cubenol	C74	
			α -Murolool	C75	
			α -Cadinol	C76	
			Selin-11-en-4- α -ol	C77	
			<i>cis</i> -Calamene-10-ol	C78	
			Eremophilone	C79	
<i>Calea harleyi</i> H. Rob.	Brazil	Air-dried plant material	8-Desacetylchaptiatriin 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	
			1,2-Dihydroxy- 3,4-dehydromenthone	C84	
<i>Calea hispida</i> (DC.) Baker	Brazil	Air-dried plant material	5 β -Myrtenyl-9 α -hydroxy-4,5-dihydroatripliciolide-8-O-angelate	C85	Bohlmann et al. (1982f)
			5 β ,9 α -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	
<i>Calea hymenoleps</i> Baker.	*NR	Air-dried plant material	8-O-Dihydrocaleteucrin acetate	C89	Bohlmann et al. (1982c)
			Calelepin seneciolate	C90	
			Caleahymenone A	C91	
			Caleahymenone B	C91	
			Isoatripliciolide angelate	C93	
			Caleamyrcenolide	C94	
<i>Calea integrifolia</i> (DC.) Hemsl.	Mexico		Heptadeca-2- <i>t</i> -9,16-trien-1-al	C95	Bohlmann and Zdero (1977a)
<i>Calea jamaicensis</i> (L.) L.	Jamaica	Leaves, Flowers, Stem	Jamaicolide A	C96	Ober et al. (1985d)
			Jamaicolide B	C97	
			Jamaicolide C	C98	
			Jamaicolide D	C99	
<i>Calea lantanooides</i> Gardner	Brazil	Aerial parts	15-Deoxybudlein A	C100	Vichnewski et al. (1982)
<i>Calea leptoccephala</i> S.F. Blake	Mexico	Leaves, Flowers, Stem	8 β -Angeloyloxy-9 α -acetoxycalculatolide	C101	Ober et al. (1986)
			Desacetylcalein A	C102	
			8 β -Angeloyloxyleptocephalide	C103	
<i>Calea megacephala</i> B.L. Rob. & Greenm.	Mexico	Leaves, Flowers, Stem	Desacylisovalerylheliangine	C104	Ober et al. (1987b)
			8 β -Methacryloyloxytemifolin	C105	

Table 1. Cont'd.

<i>Calea morii</i> H. Rob.	Brazil	Air-dried plant material	2,3-Dimethyl-6-(acetoxyl-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	
			3 β -Acetoxy-8 β -angeloyloxy-1,10-dihydro-1 α ,10 β -epoxycostunolide	C111	
			5-Myrtenyl-4,5-11,13-tetrahydro-11,13-epoxyatripliciolide-8-O-angelate	C112	
<i>Calea nelsonii</i> 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-9,10-diisobutyryloxythymol	C116	
			7-Isobutyryloxy-8,9dihydroxythymol	C117	
			8,9-epoxy-7-isobutyryloxythymol isobutyrate	C118	
<i>Calea oxylepis</i> Baker	Brazil	Air-dried plant material	1 β -Hydroxy-8-desacylzacatechinolide-(2-methylbutyrate)	C119	Bohlmann et al. (1982a)
			1 α -Acetoxy-8-desacylzacatechinolide-(2-methylbutyrate)	C120	
			1-Oxo-8-desacetylzacatechinolide-(2-methylbutyrate)	C121	
			1,2-Diacetoxy-1,2-dihydroartemisia alcohol acetate	C122	
<i>Calea peckii</i> B.L. Rob.	Costa Rica	Leaves, Flowers	4,6-Dimethoxy-2-isopropylidene-3oxo-2,3-dihydrobenzofurane	C123	Castro et al. (1989)
			1 β -Hydroxy-Bisabola-2,10-dien-4-one	C124	
			1 α -Hydroxy-Bisabola-2,10-dien-4-one	C125	
			4-Hydroxy-3methoxybisabola-1,10-diene	C126	
			1 α -Hydroxy-8 β -tigloyloxyguaia-3,9,11(13)-trien-1,2,6 α -olide	C127	
			3 β -Hydroxy-8 β -tigloyloxyheliangolide	C128	
<i>Calea pilosa</i> Baker	Brazil	Air-dried plant material	2-[2-Acetoxyethyl]-5-prop-1-ynyl-dithienyl	C129	Bohlmann et al. (1981a)
			Atripliciolide angelate	C130	
			9 α -Hydroxyatripliciolide-8-O-angelate	C131	
			9 α -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	
			9 α -Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-angelate	C134	
			9 α -Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-tiglate	C135	
			9 α -Hydroxy-11,13-dihydro-11,13-epoxyatripliciolide-8-O-methacrylate	C136	
			11-Hydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-angelate	C109	
			9 α ,11-Dihydroxy-13-chloro-11,13-dihydroatripliciolide-8-O-angelate	C137	
			3 β -Acetoxy-8 β -angeloyloxy-1,10-dihydro-1 α ,10 β -epoxycostunolide	C111	
5-Myrtenyl-4,5-11,13-tetrahydro-11,13-epoxyatripliciolide-8-O-angelate	C112				

Table 1. Cont'd.

<i>Calea pinnatifida</i> (R. Br.) Less.	Brazil	Aerial parts	4-Glycosyloxybenzoic acid	C138	Ferreira et al. (1980)
			Anisic acid	C139	
			Tetradeca-4E,6E,12E-trien-8,10-diyn-1-ol	C140	
			Arucanolide	C141	
	Brazil	Leaves	6-Acetyl-7-hydroxy-2,2-dimethylchromene	C142	Lima et al. (2015a)
			6-Acetyl-7-methoxy-2,2-dimethylchromene	C143	
			6-(1-Hydroxyethyl)-7-methoxy-2,2-dimethylchromene	C144	
			6-(1-Ethoxy)-7-methoxy-2,2-dimethylchromene	C145	
	Brazil	Leaves	Ethyl caffeate	C146	Lima et al. (2016)
			Vanilin	C147	
12-hydroxy-encecalin			C148		
Phytol			C149		
3,4-di-O-caffeoylquinic acid			C150		
3,5-di-O-caffeoylquinic acid			C151		
4,5-di-O-caffeoylquinic acid			C152		
11,13-dihydroxy-calaxin	C153				
<i>Calea platylepis</i> Sch. Bip. ex Baker	Brazil	Leaves, Flowers, Underground parts	Genkwanin	C154	Nascimento et al. (2004a)
			(+)-4 <i>l</i> ,7 <i>l</i> -Aromadendranediol	C155	
			Euparin	C156	
			Caleprunin A	C157	
			Caleprunin B	C158	
			Euparone	C159	
<i>Calea prunifolia</i> Kunth	Panama		Acacetin	C3	Ober et al. (1985b)
			Calbertolide C	C4	
			Prunichromene A	C160	
			Prunichromene B	C161	
Costa Rica	Leaves, Flowers		Caleprunin A	C157	Ober et al. (1985e)
			Caleprunin B	C158	
Costa Rica	Leaves, Flowers		4,6-Dimethoxy-2-isopropylidene-3oxo-2,3-dihydrobenzofurane	C123	Castro et al. (1989)
			7-Methoxycateurcrin	C162	
			Caleprunifolin	C163	
			2-Seneciyl-hydroxyquinone-4-O-methyl ether	C164	
			5 α -Hydroperoxy-costol acetate	C165	
Colombia	Leaves		1-(2-Hydroxy-5-(1-methoxyethyl)phenyl)-3-methylbut-2-en-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	C168	Puebla et al. (2011)
			3,5-Di-O-[E]-caffeoylquinic acid	C169	
			ent-15b-(β -D-Glucopyranosyloxy)-kaur-16-en-19-oic acid β -D-glucopyranosyl ester	C170	
<i>Calea reticulata</i> Gardner	Brazil	Air-dried plant material	Germacra-4(15), 5, 10(14)-trien-1-one	C171	Bohlmann et al. (1982b)
			6-Epi- β -verbesinol coumarate	C172	
			1 β ,10 α -Epoxy-8 β -tiglinoyloxy-1,10-dihydrocostunolide	C173	Bohlmann et al. (1981b)
			Heliangin-3-O-acetate	C174	
<i>Calea rotundifolia</i> (Less.) Baker	Brazil	Air-dried plant material	8 β -Tiglinoyloxyreynosin	C175	
			1 β -Hydroxy-8 β -tiglinoyloxyarbusculin B	C176	
			8 β -Tiglinoyloxybalchanin	C177	
			3-Hydroxy-octa-1,5t-dien-7-one	C178	
<i>Calea rupicola</i> Chodat	Paraguay	Leaves, flowers, Stem, roots	9 α -Hydroxyatripliciolide-8-O-isobutyrate	C179	Schmeda-Hirschmann et al. (1986)
			5 β -Myrtenyl-4 α ,5-dihydroatripliciolide-8-O-isovalerate	C180	
	Brazil	Aerial parts	Eupatoriochromene	C181	Steinbeck et al. (1997)
			Precocene II	C182	
<i>Calea serrata</i> Less.			Precocene II	C182	Ribeiro et al. (2011)
	Brazil	Leaves	Sesquiterpene hydrocarbons germacrene D	C183	
		Stems	β -Selinene	C62	
			Bicyclogermacrene	C184	
	Venezuela	*NR	Acacetin	C3	Ober et al. (1985c)
			Heliangine	C185	
			Calbertolide C	C4	
<i>Calea solidaginea</i> Kunth			8-Epi-8-tiglylrupicolin A	C6	
			Desacyl-8-tiglylsuvcordatolide A	C5	
	Venezuela	Leaves, flowers, stem, roots	Solidaginolide A	C186	Ober et al (1985c)
			Solidaginolide B	C187	
	Venezuela	Air-dried plant material	8-Epi-isobutyrylrupicolin A	C188	Ober et al. (1984c)
			8-Epi-isobutyrylrupicolin B	C189	
			Subcordatolide A	C190	Ober et al. (1984d)
	Venezuela	Air-dried plant material	Subcordatolide B	C191	

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	9 α -Acetoxyzexbrevin 9 α -Hydroxy-11,13-dihydro-11 α ,13-epoxyatripliciolide-8 β -O-[2-methylacrylate] 9 α -Hydroxy-11,13-dihydro-atrilociolide-8 β -O-[2-methylacrylate]	C195 C196 C197	Lee et al. (1982b)
<i>Calea temifolia</i> var. <i>calyculata</i> (B.L. Rob.) Wussow, Urbatsch & G.A. Sullivan	Mexico	Dried leaves	8 β -Angeloyloxy-9 α -acetoxysterfolin 8 β -Angeloyloxy-9 α -[2-methylbutanoyloxy]-ternifolin	C198 C199	Lee et al. (1982a)
	Mexico	Dried aerial parts	8 β -Angeloyloxy-9 α -hydroxycalyculatolide 8 β -Methylacryloyloxy-9 α -hydroxycalyculatolide 15-Hydroxy-11,13-dihydro-11 α , 13-epoxyatripliciolide-8 β -O-angelate	C200 C201 C202	Fischer et al. (1984)
<i>Calea teucrifolia</i> (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)
<i>Calea trichomata</i>	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-Seneciyl-4-(hydroxyethyl)-phenol 2-Seneciyl-4-(angeloyloxyethyl)-phenol 2-seneciyl-4-(methoxyethyl)-phenol 2-seneciyl-4-(pentadecanoyloxyethyl)-phenol	C211 C212 C213 C214	Nascimento et al. (2004b)
<i>Calea uniflora</i> 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)
			6-Methoxy-isoeugenol-isobutyrate	C225	
			Caleurticin	C226	
			9 α -Hydroxy-atrilociolid-8-O-[2-methylacrylate]	C227	
	*NR	Leaves	9 α -[Isovaleryloxy-bzm. Senecioyloxy-bzw. Angeloyloxy]-15-hydroxy-atrilociolid-8-O-[2-methylacrylate]	C228	Bohlmann and Jakupovic (1979)
			Caleurticolidacetate	C229	
			Caleurticolide-[2-methylacrylate]	C230	
			Caleurticolide-angelicate	C231	
<i>Calea urticifolia</i> DC.	El Salvador	Dried leaves	Juanislamin	C232	Castillo et al. (1981)
			2,3-epoxy-juanislamin	C233	Ohguchi et al. (2009)
			Calealactone A	C234	
			Calealactone B	C235	
			Calealactone C	C236	
		Leaves	2,3-epoxy-calealactone A	C237	Yamada et al. (2004)
	Mexico		Calein D	C238	Ohguchi et al. (2009)
			Juanislamin	C232	
			2,3-epoxy-juanislamin	C233	
		Leaves	Arucanolide	C141	Ohguchi et al. (2009)
<i>Calea villosa</i> Baker	Brazil	Air-dried plant material	8 β -Angeloyloxy-3 β -(2-methylbutyryloxy)-1 β ,10 α -epoxy-1,10H-costunolide	C239	Bohlmann et al. (1982e)
			11,13-Epoxy-11,13H-budlein A	C240	
			11 β -Hydroxy-13-chloro-11,13H-budlein A	C241	
	*NR	Aerial parts	1 α -Acetoxy-zacatechinolide	C242	Bohlmann and Zdero (1977b)
			1-Oxo-zacatechinolide	C243	
<i>Calea zacatechichi</i> Schlttdl.	*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	
	*NR	Leaves,Stems	Calealactone C	C236
			Calealactone D	C254
			Calealactone E	C255
			8 β -angeloxy-9 α -acetyloxycalculatolide	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-H₂O 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 IC₅₀ values between 6 and 25 μ g/ml. All flavones isolated from *C. zacatechichi* had activity against *Plasmodium falciparum*, with IC₅₀ values ranging from 4 to 40 μ M (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

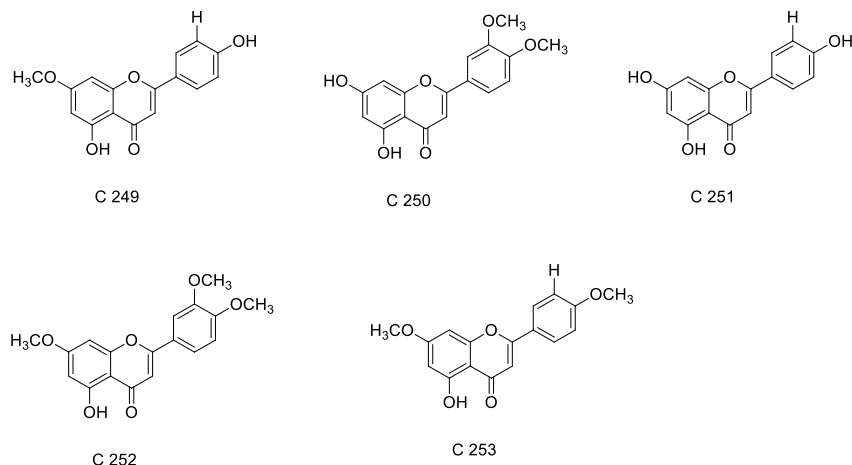


Figure 1. Flavonoids isolated from *Calea zacatechichi* with antiplasmodial activity.

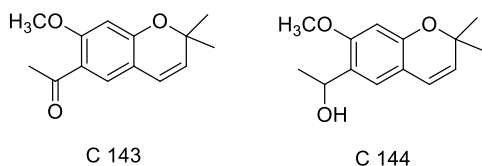


Figure 2. Chromenes of *Calea pinnatifida* with *in vitro* leishmanicidal activity.

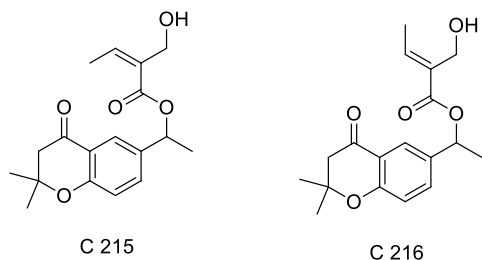


Figure 3. Chromanones isolated from *Calea uniflora* with leishmanicidal activity.

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 μ g/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), 8 β -angeloxy-9 α -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-Senecioid-4-(hydroxyethyl)-phenol (C211), 2-Senecioid-4-(angeloyloxyethyl)-phenol (C212), 2-senecioid-4-(methoxyethyl)-phenol (C213) and 2-senecioid-4-(pentadecanoyloxyethyl)-phenol (C214) (Table 1 and

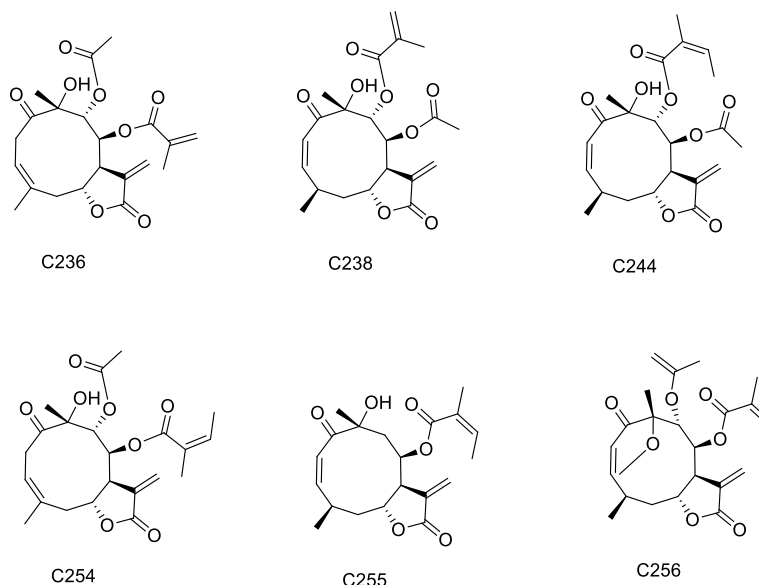


Figure 4. Sesquiterpene lactones isolated from *Calea zacatechichi* with leishmanicidal activity.

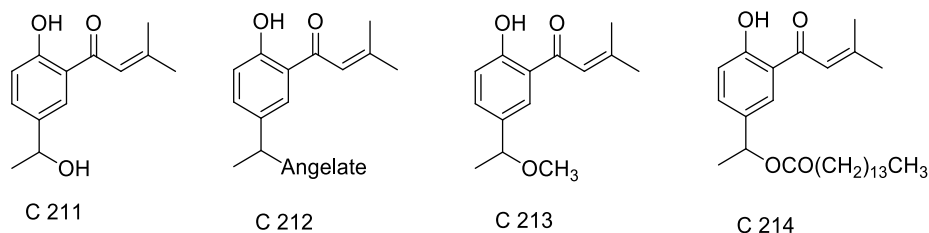


Figure 5. *p*-hydroxyacetophenone derivatives from *Calea uniflora* with trypanocidal properties.

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 $\mu\text{g/ml}$ (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 clauseniana* 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:

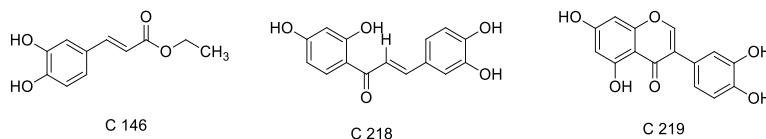
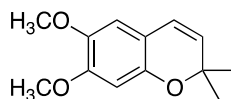


Figure 6. Phenolic compounds of *Calea uniflora* with trypanocidal activity.



C 182

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 ($1 \mu\text{g mL}^{-1}$), both mixtures (1:1:1) and the EtOH extract exerted preventive anti-adrenergic activity increasing the phenylephrine CE₅₀ 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-methylbut-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 CH₂Cl₂ 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 anti-inflammatory 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-

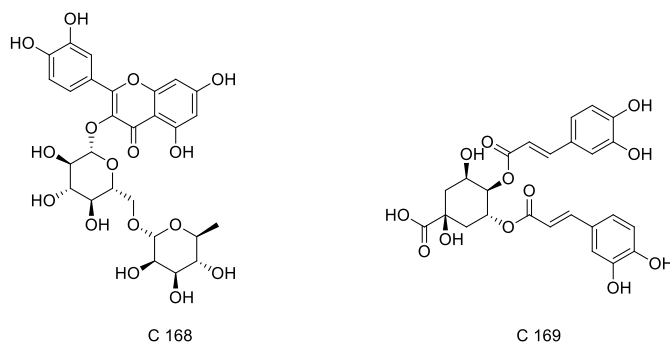


Figure 8. Phenolic compounds from *Calea prunifolia* with vasodilator activity.

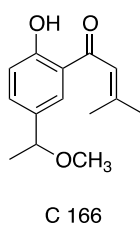


Figure 9. *p*-hydroxyacetophenone derivative isolated from *Calea prunifolia* with anti-inflammatory activity.

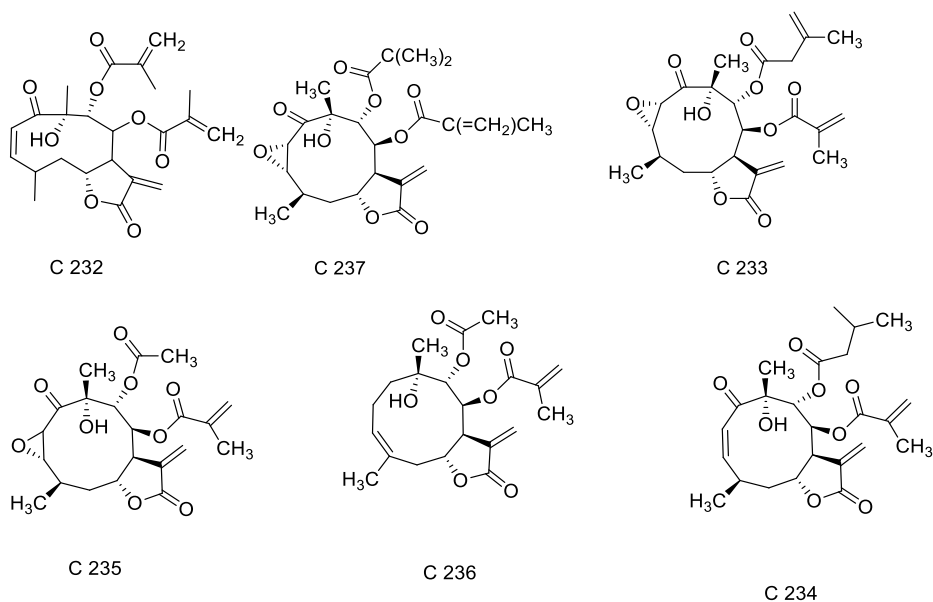


Figure 10. Sesquiterpene lactones from *Calea urticifolia* tested for cytotoxic activity.

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 potent inhibitory activity on melanogenesis through

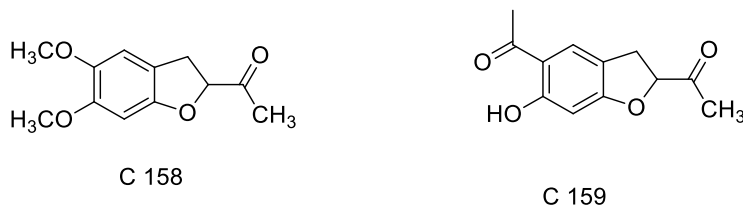


Figure 11. Benzofurans isolated from *Calea platylepis* with antimicrobial activity.

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 melanoma 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 (+)-4 α ,7 β -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 mentagrophytes* 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 IC₅₀ 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 constituents.

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.

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