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Review Article

The genus *Cordia*: botanists, ethno, chemical and pharmacological aspects

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ABSTRACT

Species of the genus *Cordia*, Boraginaceae, are widely studied with regard to the various ethnobotanical and ethnopharmacological aspects. They are found principally in tropical and subtropical regions of the American, Asian and African continents, where they occur in various countries. In the genus *Cordia*, there are many species cultivated for ornamental plants, wood and medicinal applications, where they are extensively utilized by traditional communities. In the last decades, scientific studies of *Cordia* species have intensified, demonstrating the great interest in phytochemical, biological and pharmacological studies. In this review, we describe the principal botanical aspects, ethnopharmacological information and evaluation of the bioactive and pharmacological properties of *Cordia*, its phytochemical constituents and the most common classes of secondary metabolites identified. The information reported in this work contributes scientifically to recognizing the importance of the genus *Cordia* as a target in the search for new biotechnological investments.

Introduction

Although reports of the first civilizations pointed out the curative potential of the plants, only in the last decades has there been a true and growing interest in evaluating and establishing their chemical and pharmacological properties. A variety of research groups from widely varying sectors, such as industry, institutes and research in the chemistry and pharmacology of plants, have been working on a more concrete understanding of the true therapeutic properties and discovery of new substances that can be utilized as active principles in the treatment of diseases (Novais et al., 2003).

The first reports of the genus *Cordia*, Boraginaceae included botanical and reproductive characteristics. The plants were characterized as being fertile, because they are incapable of self-fertilization, which is an important criterion for the identification of the species belonging to the genus (Bawa, 1974; Boshier, 1995; Gibbs and Taroda, 1983; Machado and Loiola, 2000; Melo and Andrade, 2007; Opler et al., 1975).

The genus *Cordia* encompasses about 250 species; the majority are tree- or shrub-sized and native to the Americas, and they occur from Central America down to the central region of Argentina (Barroso and Oliveira, 2009; Corrêa, 1984).

In popular medicine, the species of the genus *Cordia*, are reported as plants utilized for the treatment of various illnesses that affect many human systems. Box 2 lists the various ethnopharmacological applications, which are notably for antimicrobial, antiinflammatory, anthelmintic, analgesic and diuretic purposes and for treating digestive system, respiratory, urogenital, cardiac, vascular and blood disorders (Akisue et al., 1983; Arrebola et al., 2004; Bhattacharya and Saha, 2013; Biavatti et al., 2007; Costa et al., 2008; Matias et al., 2010b; Medeiros et al., 2007; Menezes et al., 2001; Oliveira et al., 2012a; Paulino et al., 2011a; Scheeren et al., 2002; Sertié et al., 1990).

Due to the various ethnopharmacological reports attributed to species of the genus *Cordia*, numerous research groups have conducted studies to prove their pharmacological or biological properties through a variety of methods and assays *in vitro* and *in vivo* of pre-clinical nature, which are described in Box 2. There are published reports describing through a wide variety of methods their diverse activities: antimicrobial, antibiotic-modifying, antiinflammatory, antinociceptive, antifertility, toxicity, anti-snake bite, hypolipidemic, immunomodulatory, insecticidal and antioxidant

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(Al-Musayeib et al., 2011; Bayeux et al., 2002; Bhattacharya and Saha, 2013; Caparroz-Assef et al., 2008; Cardozo et al., 2008; Costa et al., 2008; Matias et al., 2010b, 2013a; Panghal et al., 2011b; Salazar-Aranda et al., 2011; Ticli et al., 2005).

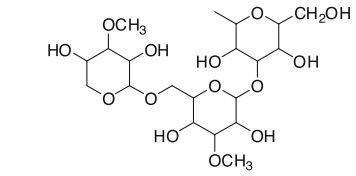
Various research groups have carried out phytochemical studies resulting in the identification of different classes of secondary metabolites, as well the isolation of various constituents of different parts (root, stem, leaves, flowers and fruits) of various species of the genus *Cordia*, as described in Box 1.

Box 1: List of identified substances of *Cordia* reported in the literature in chronological order.

Species (part used)	Substance	Reference
C. verbenacea (leaves)	Cordialin A (**1**)	Velde et al. (1982)
C. myxa (leaves)	α-Linolenic acid (**2**) Linoleic acid (**3**) Oleic acid (**4**)	Wassel et al. (1987) Miralles et al. (1989)
C. macleodii (leaves and flowers)	*p*-Hydroxyphenylacetic acid (**5**) Quercetin (**6**)	El-Sayed et al. (1998)
C. trichotoma (stem)	Trichotomol (**7**) Cordiachrome C (**8**) α-Cadinol (**9**) Oleanolic acid (**10**) Oncocalyxone A (**11**) β-Sitosterol β-Sitosterol-β-D-glucoside Allontoin (**12**) Saccharose	Menezes et al. (2001) Dini et al. (2001)
C. multispicata (leaves)	Cordianol A (**13**)	Kuroyanagi et al. (2001)

Box 1 (*Continued*)

Species (part used)	Substance	Reference
C. dichotoma (leaves)	Arabinoglucan (**14**) γ-Linolenic acid (**15**)	Guil-Guerrero et al. (2003)
C. verbenacea (leaves)	α-Humulene (**16**) *Allo*-aromadendrene (**17**) *Trans*-caryophyllene (**18**)	Douglas et al. (2004) Ticli et al. (2005)
C. trichotoma (stem)	α-Cadinol (**19**) α-Muurolol (**20**) *epi*-α-Muurolol (**21**)	Sylvestre et al. (2006) Lago et al. (2006)
C. verbenacea (leaves)	Rosmarinic acid (**22**) α-Pinene (**23**)	Fernandes et al. (2007) Sartorelli et al. (2007)
C. verbenacea (leaves)	1,8-Cineole (**24**) δ-Elemene (**25**) β-Elemene (**26**)	Medeiros et al. (2007)
C. globosa (leaves)	5-Hydroxy-4′,7-dimethoxyflavanone (**27**) Eriodictiol (**28**)	Silva et al. (2010)



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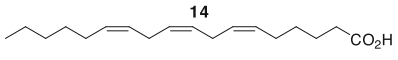

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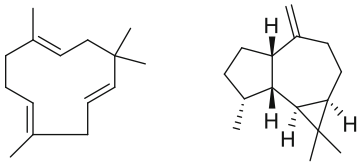
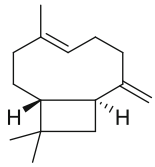


16 **17**



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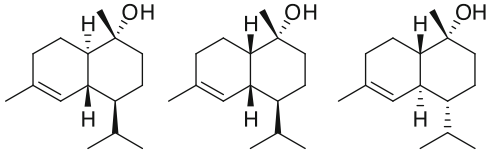
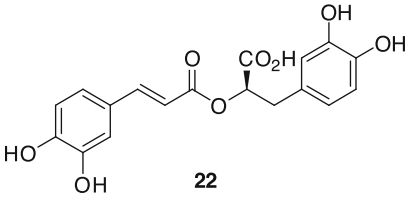


19 **20** **21**



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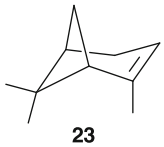

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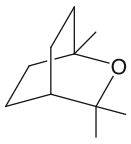

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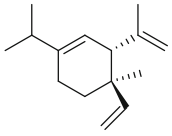

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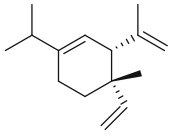

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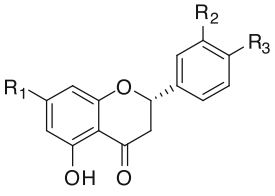
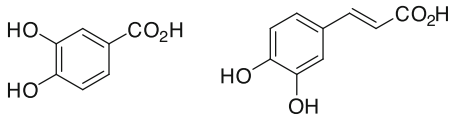
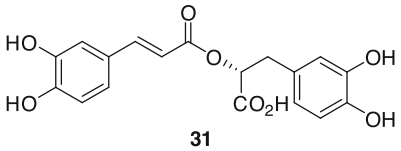
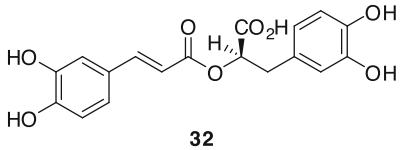
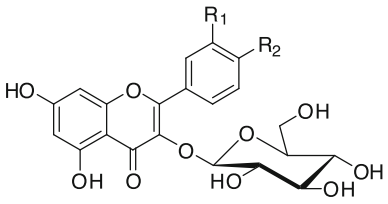
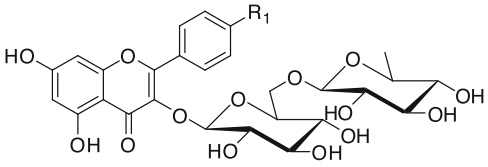
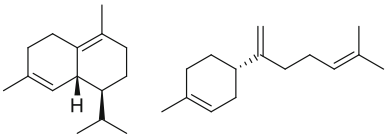
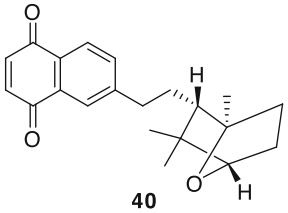
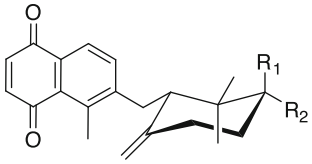
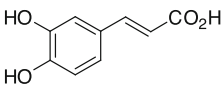
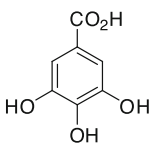


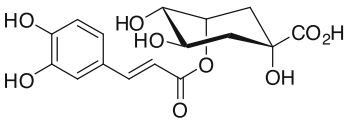
27 R_1=R_3=OCH_3; R_2=H
28 R_1=R_2=R_3=OH

Box 1 (*Continued*)

Species (part used)	Substance		Reference
C. sinensis (leaves)	Protocatechuic acid (**29**) *Trans*-caffeic acid (**30**) Methyl rosmarinate (**31**) Rosmarinic acid (**32**) Kaempferide-3-*O*-β-D-glucopyranoside (**33**) Kaempferol-3-*O*-β-D-glucopyranoside (**34**) Quercetin-3-*O*-β-D-glucopyranoside (**35**) Kaempferide-3-*O*-α-L-rhamnopyranosyl (1→6)-β-D-glucopyranoside (**36**) Kaempferol-3-*O*-α-L-rhamnopyranosyl (1→6)-β-D-glucopyranoside (**37**)	 **29** **30**  **31**  **32**  **33** R_1=H; R_2=OCH_3 **34** R_1=H; R_2=OH **35** R_1=R_2=OH  **36** R_1=H; R_2=OCH_3 **37** R_1=H; R_2=OH	Al-Musayeib et al. (2011) de Souza et al. (2011) Qu et al. (2011) Xiao et al. (2011)
C. verbenacea (leaves)	δ-Cadinene (**38**) β-Bisabolene (**39**)	 **38** **39**	de Souza et al. (2011) Pinhol et al. (2012)
C. leucocephala (roots)	(11*S*,13*S*,16*R*)-Cordiaquinone J (**40**) 6-[10-(12,12-Dimethyl-13α-hydroxy-16-methenyl-cyclohexyl)ethyl]-1,4-naphthalenedione (**41**) 5-Methyl-6-[10-(12.12-dimethyl-13β-hydroxy-16-ciclohexil)methyl-1,4-naphthalenedione (**42**)	 **40**  **41** R_1=OH; R_2=H **42** R_1=H; R_2=OH	Oliveira et al. (2012b) Rodrigues et al. (2012)
C. verbenacea (leaves)	Caffeic acid (**43**) Gallic acid (**44**) Chlorogenic acid (**45**)	 **43**  **44**	Matias et al. (2013b) Matias et al. (2013c)

Box 1 (*Continued*)

Species (part used)	Substance	Reference
C. dichotoma (leaves)	Luteolina (**46**) Apigenin (**47**) Hentricontanol (**48**) Hesperidine (**49**) Octasanole (**50**) Lupeol (**51**) α-Amyrin (**52**) Robonine (**53**) Rutin Betulin (**54**) Dihydrorobenetin (**55**)	Bhattacharya and Saha (2013) Hussain and Kakoti (2013) Jamkhande et al. (2013)



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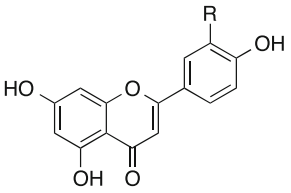
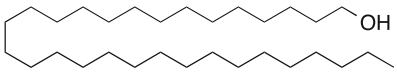


46 R=OH
47 R=H



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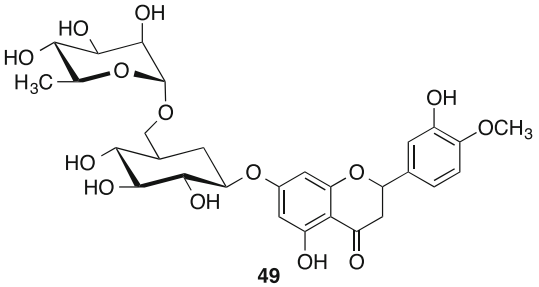

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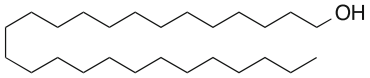

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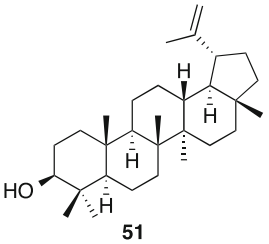

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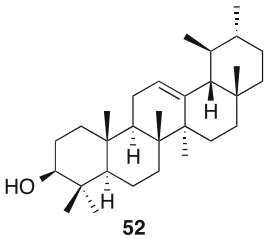

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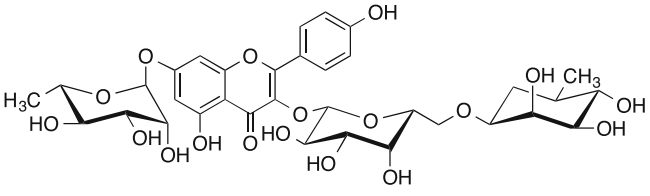

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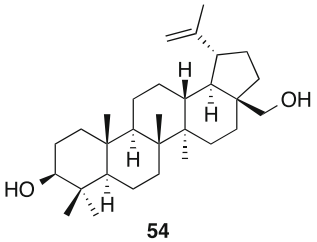

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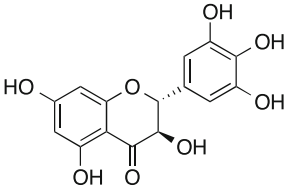

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The objective of this review was to discuss the principal chemical, biological and pharmacological aspects of the species of the genus *Cordia*, featuring the compounds identified and their biological or pharmacological properties. We emphasize that this review is an update report on the genus *Cordia* and will serve as the foundation for new investigations aimed at obtaining more details about the plants of this important botanical genus.

Material and methods

The study was carried out in the following databases: Pubmed, Scielo, Web of Science, Scirus, Bireme and Science Direct, with updating until March 2014, using as search terms the key words and combinations: *Cordia*, natural product, chemical composition, ethnopharmacological activity, pharmacological activity, biological activity.

Occurrence and distribution

The genus *Cordia* shows an occurrence and distribution in areas with tropical and subtropical climate in Central and South America, India, Asia and Africa. The species of the genus *Cordia* are especially included in studies of natural products of plant origin due to their diversity of chemical, biological and pharmacological properties (Matias et al., 2010a,b).

The principal species reported in databanks on the genus *Cordia* are: *C. abyssinica* R. Br., *C. africana* Lam., *C. alliodora* (Ruiz & Pav.) Oken, *C. corymbosa* Willd. ex. Roem. & Schult., *C. curassavica* (Jacq.) Roem. & Schult., *C. cylindrostachya* Roem. & Schult., *C. dentata* Poir., *C. dichotoma* G. Forst., *C. ecalyculata* Vell., *C. flavescens* Aubl., *C. fragrantissima* Kurz., *C. francisci* Ten., *C. globosa* (Jacq.) Kunth., *C. goeldiana* Gürke., *C. latifolia* Roxb., *C. leucocephala* Moric., *C. linnaei* Stearn., *C. macleodii* Hook. F. & Thomson, *C. martinicensis* (Jacq.) Roem. & Schult., *C. monosperma* (Jacq.) Roem. & Schult., *C. multispicata* Cham., *C. myxa* L., *C. nodosa* Lam., *C. oblique* Willd., *C. oncocalyx* Fr. All., *C. piauhienses* Fresen., *C. tothii* L., *C. rufescens* A.DC., *C. salicifolia* Cham., *C. sellowiana* Cham., *C. sinensis* Lam., *C. superba* Cham., *C. thaisiana* G. Agostini, *C. trichotoma* (Vell.) Arráb. ex Steud. e *C. verbenacea* DC.

C. trichotoma, popularly known as "louro-pardo," is distributed in Brazil from Ceará to Rio Grande do Sul states, but can also be found in Argentina, Paraguay and southern Bolivia. It is extensively utilized as an ornamental plant and is indicated principally for reforestation and recovery of degraded areas (Freitas et al., 2006, 2008; Mendonça et al., 2001; Souza, 2008). *C. curassavica* occurs in Brazil from the Amazon region to the state of Rio Grande do Sul, normally 500–1000 m from the shoreline (Bayeux et al., 2002). *C. dichotoma*, known popularly as Indian cherry is a small shrub with globous fruits, yellowish brown, black or rose. It is found in India and other regions with warmer climate (Scheeren et al., 2002). *C. piauhiensis* and *C. tothii* are endemic to Brazil and distributed in the South, Southwest, Southeast and Northeast regions (Santiago et al., 2005). *C. verbenacea*, known popularly as erva baleeira is found in Brazil along its costal region (Medeiros et al., 2007; Pimentel et al., 2012), but is also found in Central America and in central region of Argentina, since it is a native plant of the Americas (Rosa et al., 2008). *C. obliqua* is a fruit tree found in various countries on the Indian continent, where its fruits are greatly appreciated by the local population (Mukherjee et al., 2008). *C. rufescens* is a shrub found in Northeast Brazil (Costa et al., 2008). *C. salicifolia* and *C. ecalyculata* can be found in Brazil, most often from the state of Minas General to Rio Grande do Sul, where it is found even in Acre and Brasilia (Alves et al., 2004) but it can also occur in tropical forest areas of Argentina and Paraguay (Cardozo et al., 2008; Siqueira et al., 2006). *C. dentata*e is localized in the tropical forests of the Colombian Caribbean region and is utilized as a food source in the dry period (Garcia et al., 2009). *C. sellowiana* and *C. myxa* are species found in the temperate regions of the whole world and in the tropics (Barroso et al., 2009). *C. flavescens*, *C. globosa* and *C. goeldiana* are widely distribute in various regions including: Florida, Caribbean, Central America and northeastern South America, it is limited to the Caatinga (Machado et al., 2010). *C. laurecea* and *C. leucocephala* are species endemic to Northeast Brazil and are widely cultivated for ornamental purposes (Machado et al., 2010; Milet-Pinheiro and Schlindwein, 2010). *C. macleodii* and *C. nodosa* have a wide distribution in tropical America (Izzo and PetInI-BenellI, 2011). *C. sinensis*, *C. superba* and *C. thaisiana* are found in the drier areas of India, Africa and Saudi Arabia (Al-Musayeib et al., 2011; Araque et al., 2009). *C. abyssinica*, *C. africana*, *C. alliodora* are species that have wood utilized in production of high-quality furniture and other objects and domestic utensils. It is highly valued commercially in Ethiopia, and it is also a native species of Saudi Arabia and tropical Africa (Derero et al., 2011).

Chemical components

Studies aimed at identifying new phytotherapeutic compounds in species of the genus *Cordia* have led to the qualification of various classes of secondary metabolites and to the isolation of a number of compounds belonging to various classes (Box 1).

Traditional application and biological/pharmacological activities attributed to genus *Cordia*

Box 2 lists the species of the genus *Cordia* with the ethnopharmacological reports described by traditional people and biological/pharmacological activities tested. *C. trichotoma* shows a diversity of applications in popular medicine such as for antiinflammatory, wound-healing, anthelmintic, antimalarial and diuretic purposes and in the treatment of pulmonary diseases, urinary infections and leprosy (Menezes et al., 2001). The ethnopharmacological properties of *C. dichotoma* have been described since ancient times, where its seeds have been utilized for antiinflammatory purposes and its fruits as expectorant, laxative, diuretic and anthelmintic medicines (Scheeren et al., 2002). *C. myxa* is described in popular medicine as laxative and cough medicine in pulmonary diseases (Arrebola et al., 2004). *C. salicifolia* and *ecalyculata* are used as an anorexic, diuretic, appetite suppressant (in the treatment of obesity), cardiotonic, and aid to reduce blood levels of triglycerides and cholesterol (Alves et al., 2004; Caparroz-Assef et al., 2008; Cardozo et al., 2008). *C. rufescens* is used in medicine popular as an abortifacient and antiinflammatory (Costa et al., 2008). The stem bark of *C. sinensis* is used in traditional medicine for the treatment of gastric and respiratory disturbances (Al-Musayeib et al., 2011). *C. globosa* is utilized in traditional medicine in Paraiba State, Brazil for digestive problems, rheumatism and menstrual colic. In the Xingo region of Alagoas State, its leaves and flowers are used for the treatment of hemorrhaging, throat infections and cold (Paulino et al., 2011b, 2012). The leaves and roots of *C. leucocephala* are used in popular medicine for digestive disturbances, rheumatism and as a general tonic (Oliveira et al., 2012a). Besides the treatment of symptoms of menstrual colic and dyspepsia (Silva et al., 2010). *C. verbenacea* has aromatic leaves that with biological activity for their antimicrobial (Matias et al., 2010a,b, 2013a,b), antiinflammatory, antirheumatic, analgesic, and tonic properties (Lameira et al., 1997; Medeiros et al., 2007) and arthritis (Costa et al., 2008). The leaves and stem of *C. curassavica are* used for various superficial inflammatory processes in wound areas and general inflammations and also as an analgesic for menstrual colic (Bayeux et al., 2002). The leaves of *C. flavescens*

Box 2: List of the genus *Cordia* applied and evaluated in traditional, chronologically related biological activities medicine.

Species	Ethnopharmacological applications and biological and/or pharmacological activity	Reference
C. myxa	Analgesic Anti-inflammatory Antimicrobial	Tiwari and Srivastava (1967) Rimando et al. (1987)
C. goetzei	Antifungal	Marston et al. (1988)
C. verbenacea	Antimicrobial	Sertié et al. (1990) Sertie et al. (1991)
C. dichotoma	Nutritional	Duhan et al. (1992)
C. corymbosa	Antimicrobial	Silva Filho et al. (1993)
C. latifólia	Anti-ulcer Anti-histamine	Akhtar and Ahmad (1995)
C. myxa	Analgesic	Ficarra et al. (1995)
C. verbenacea	Analgesic Anti-inflammatory	Lameira et al. (1997)
C. myxa	Antimicrobial	Carvalho and Marchini (1999)
C. alliodora	Antifungal Larvicidal	Ioset et al. (2000)
C. trichotoma	Antimicrobial Anthelmintic Anti-inflammatory Antimalarial Healing Diuretic Respiratory system disorder Urogenital system disorder	Menezes et al. (2001)
C. multipicata	Antiandrogen	Kuroyanagi et al. (2001)
C. curassavica	Antinociceptive Anti-inflammatory	Bayeux et al. (2002)
C. curassavica	Anti-inflammatory	Bayeux et al. (2002)
C. dichotoma	Anti-inflammatory Anti-helminth Diuretic Digestive system disorder Respiratory system disorder	Scheeren et al. (2002)
C. myxa	Digestive system disorder	Arrebola et al. (2004)
C. ecalyculata	Respiratory system disorder	Alves et al. (2004)
C. verbenacea	Fetal toxicity	Carvalho-Júnior et al. (2004)
C. salicifolia *C. verbenacea*	Toxicological Antiophidic Analgesic	Caparroz-Assef et al. (2008) Ticli et al. (2005)
C. salicifolia	Diuretic Cardiovascular system disorder Digestive system disorder	Caparroz-Assef et al. (2008)
C. salicifolia	Hypolipidemic	Siqueira et al. (2006)
C. verbenacea	Anti-inflammatory	Medeiros et al. (2007)
C. salicifolia	Diuretic Cardiovascular system disorder Digestive system disorder hypolipidemic	Cardozo et al. (2008)
C. superba *C. rufescens*	Abortive Anti-inflammatory Immunomodulatory	Costa et al. (2008)
C. verbenacea	Bone/muscle system disorder	Matias et al. (2010b)
C. verbenacea	Antibacterial	Matias et al. (2010c) Matias et al. (2010d)
C. dichotoma	Anti-inflammatory	Sharma and Asati (2010)
C. globosa	Analgesic Antibacterial Antihemorrhagic Digestive system disorder Bone/muscle system disorder	Paulino et al. (2011b)
C. boissieri	Antibacterial Antifungal Antioxidant	Salazar-Aranda et al. (2011)
C. dichotoma	Antibacterial Antifungal	Panghal et al. (2011a) Nariya et al. (2011)
C. sinensis	Anti-inflammatory Antioxidant	Al-Musayeib et al. (2011)
C. sinensis	Digestive system disorder Respiratory system disorder	Al-Musayeib et al. (2011)
C. leucocephala	Analgesic Digestive system disorder Bone/muscle system disorder	Oliveira et al. (2012a)
C. verbenacea	Antibacterial	Pinhol et al. (2012)
C. verbenacea	Insecticide	Knaak et al. (2012)
C. verbenacea	Bacterial resistance modulator to antibiotics	Matias et al. (2013c) Matias et al. (2013b)
C. curassavica	Analgesic	Bhattacharya and Saha (2013)
C. flavescens	Urogenital system disorder	Bhattacharya and Saha (2013)
C. dichotoma	Analgesic Antifertility Antiglycemic Anti-helminth Antimicrobial Antiulcerogenic	Bhattacharya and Saha (2013) Jamkhande et al. (2013)
C. rothii	Immunomodulatory	Firdous et al. (2014)

are used as an analgesic for postpartum pain (Bhattacharya and Saha, 2013).

Ethnopharmacological studies are important for initiating pharmacological tests aimed at proving the possible applications of natural products from plants (Matias et al., 2013b). Box 2 lists the biological activities of essential oils, extracts and fractions of *Cordia* species and pharmacological studies of isolated substances evaluated by experimental methods of this genus.

Antinociceptive activity

In evaluated the antinociceptive activity of the dichloromethane extract of leaves and stem of *C. curassavica* by using the acetic acid-induced writhing test in rats. Six rats were used in each test group, and the extract in doses of 100, 300 and 1000 mg/kg was administered 1 h before of the injection of acetic acid. At a dose of 100 mg/kg, there was no reduction in writhings observed, while 300 mg/kg reduced the number of writhings to 17.3 ± 1.34 compared to 37.1 ± 2.28 for the control group. At 1000 mg/kg, there were even fewer writhings (13.2 ± 1.44). This biological activity was also evaluated by the hot plate test, but the dichloromethane extract did not show any activity, suggesting that the analgesic effect is limited to the inhibition of the inflammatory process (Bayeux et al., 2002).

Antibacterial activity

Studies have evaluated many species of the genus *Cordia* in relation to their antibacterial potential. Salazar-Aranda et al. (2011) carried out studies to determine the antibacterial activity of the extract of *C. boissierie*; they observed activity against Gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumonia* and *Acinetobacter baumanii*), but the extract obtained from its flowers showed significant results when tested against standard and resistant strains of *Staphylococcus aureus* analyzed the antibacterial activity of the hexane and methanolic extracts of leaves of *C. verbenacea* DC against strains of *Escherichia coli* and *S. aureus* by determining the minimal inhibitory concentration (MIC). The two extracts showed considerable antibacterial activity, where the best results were obtained with the hexane extract: MIC of 128 μg/ml for *E. coli* and 256 μg/ml for *S. aureus*. In the study of Panghal et al. (2011a) and Pinhol et al. (2012), the acetone extract of *C. dichotoma* also showed significant antibacterial activity against *S. aureus*. Another study utilizing the extract of the bark of *C. dichotoma* revealed that *E. coli* and *P. aeruginosa* were most sensitive in relation to *S. aureus* and *S. pyogenes* when evaluating the antibacterial activity of this species (Nariya et al., 2011). Evaluated the antibacterial activity of different concentrations of the standard hydroalcoholic extract, obtained from the leaves of *C. verbenacea* against *S. aureus* and *E. coli*. In the agar diffusion test, the extract in a concentration ≥400 mg/ml) inhibited the growth of *S. aureus* but not *E. coli*, which can be related to the lower susceptibility of Gram-negative bacteria to plant extracts (Pinhol et al., 2012).

Antifungal activity

Evaluated the antifungal activity of the extract of *C. boissieri* against a clinical isolate of the yeast *Candida glabrata*, utilizing the microdilution assay to determine MIC values (Salazar-Aranda et al., 2011). A MIC of 125 μg/ml was obtained, revealing that this species of *Cordia* was active against this fungus. In the study of Nariya et al. (2011), the extract of the bark of *C. dichotoma* was evaluated against three common pathogenic fungi (*Aspergillus niger*, *Aspergillus clavatus*, and *Candida albicans*) and the inhibition zone with the extract was compared with that for the conventional antifungals nystatin and griseofulvin. The results showed a notable inhibition of the growth zone of the fungi, with better results for *C. albicans* than *A. niger* or *A. clavatus*.

Toxicity

Conducted a study with the objective of obtaining safety data in relation to toxicity of the extract of *C. salicifolia*, considering the extensive use of this species in Brazilian popular medicine. In study utilized male adult rats (200–250 g) and male mice (25–30 g). The extract was administered orally or intraperitoneally. There were no deaths or other signs and symptoms of toxicity up to the highest dose tested (2000 mg/kg body weight) in mice when administered orally, and necropsy after 7 days of oral treatment with the extract also did not reveal any pathological change. Letality was observed only after intraperitoneal administration of 920 mg/kg body weight. In the rats, repeated oral administration (chronic toxicity) of different doses of extract (20, 100, 200 mg/kg) for 90 days did not produce signs characteristic of toxicity, and also, there were not deaths of the animals (Caparroz-Assef et al., 2008). The results showed low oral toxicity of the extract of *C. salicifolia* and no evidence that it poses risk after prolonged use. Phototoxicity of the methanolic extract of *C. verbenacea* was evaluated in an *in vitro* study done by Matias et al. (2010c), utilizing the bacteria *E. coli* and *S. aureus*. This species showed significant phototoxic activity against *S. aureus*, but not *E. coli*.

Antiinflammatory activity

The antiinflammatory activity of the extract of *C. dichotoma* seeds was evaluated in a study carried out by Sharma and Asati (2010), where Wistar rats weighing 160–180 g of both sexes were exposed to an inflammatory process (footpad edema) with the administration of carrageenan. One hour after the injection of this substance, the ethanolic and aqueous extracts were administered at different concentrations for each test group. The results revealed antiinflammatory activity of the extracts for all doses tested. At a dose of 500 mg/kg, the aqueous and ethanolic extracts showed maximal inhibition of edema (69.52% and 58.09%, respectively) in relation to the control group, demonstrating the efficacy of the extract of *C. dichotoma* as an antiinflammatory agent, which explains the wide use of this plant as an antiedema agent in popular medicine. Isolated nine compounds from the ethyl acetate fraction of the methanolic extract of *C. sinensis* and evaluated their antiinflammatory activity also using rats with induced inflammation (footpad edema) by the administration of carrageenan. The non-steriodal antiinflammatory diclofenac was used as the reference compound. Two compounds isolated from *C. sinensis* showed a potential and significant antiinflammatory activity: kaempferide-3-*O*-β-D-glucopyranoside (62.4%) and kaempferol-3-*O*-β-D-glucopyranoside (59.6%); they were as active as diclofenac (57.6%). Bayeux et al. (2002) demonstrated antiedematogenic activity for substances isolated from *C. curassavica* using this method. They utilized some extracts obtained from leaves and stem and the flavonoid artemitin isolated from the acetone extract of this species. The dichloromethane extract (1000 mg/kg) reduced edema by 59% after 4 h and by 68% after 5 h, while the ethanolic extract at this same concentration reduced edema by 44%, after 4 h. The petroleum ether extract did not show significant results. Study suggest that artemitin is the compound responsible for the antiinflammatory activity of this species (Bayeux et al., 2002), but in this study no antiedematogenic activity was found for this compound at doses up to 300 mg/kg. Two active compounds obtained from the essential oil of *C. verbenacea* were analyzed with regard to their antiinflammatory activity, utilizing also the experimental footpad edema model in rats in a study by Medeiros et al. (2007). These authors utilized male Wistar rats (140–180 g) treated orally with the sesquiterpenes of *C. verbenacea*: α-humulene and *trans*-caryophyllene. The two compounds showed activity, inhibiting various compounds responsible for the inflammatory process, but only α-humulene was able to prevent the production of pro-inflammatory cytokines.

Anti-snake bite activity

The methanolic extract of *C. verbenacea* inhibited significantly footpad edema induced by *Bothrops jararacussu* venom in a study by Ticli et al. (2005), where the responsible active component was isolated by Sephadex LH-20 chromatography and HPLC using a C18 column and identified as rosmarinic acid. Edema was induced by injection of 25 mg venom of *B. jararacussu* in the right footpad of male mice (18–22 g). They were also given intramuscular injections of 25 mg/50 ml of *B. jararacussu* venom or toxins in the gastrocnemius muscle to evaluate the myotoxicity of the extract. Rosmarinic acid inhibited the edema and venom-induced myotoxicity, demonstrating that this species of *Cordia* possesses potential activity against snake bite.

Activity hypolipidemica

Examined the efficacy of the extract of *C. salicifolia* in male mice (*Mus musculus*) subjected to a hyperlipidemic diet. The animals were divided into four groups: water and normal diet, water and hyperlipidemic diet, normal diet and *C. salicifolia* extract (100 mg/kg/day), and hyperlipidemic diet and *C. salicifolia* extract (100 mg/kg/day). The extract was administered by gavage for 15 days. The results showed that there was a reduction in serum total cholesterol levels in the two groups given a diet with the extract and also a significant reduction in triglyceride levels in the animals given a hyperlipidemic diet with the extract in relation to those that received a hyperlipidemic diet with water (Cardozo et al., 2008). It was therefore suggested that the diminution observed could have occurred due to the presence of components of *C. salicifolia* that exert an inhibitory action on salivary and pancreatic lipase, hindering the absorption of the triglycerides or that activate lipoprotein lipase, the enzyme responsible for the degradation of chylomicrons and VLDL. Analyzed the antihyperlipemic effect of pulverized dry leaves of *C. salicifolia* utilizing male Wistar rats weighing about 200 g. This product was dissolved in water and the solution obtained was administered (20 mg/kg/day) by gavage for 13 days. On the last day, the rats were sacrificed by decapitation and blood was obtained for cholesterol and triglyceride assays. Although there was no effect on cholesterolemia, a hypolipidemic effect was observed for this species of *Cordia* where triglyceride levels were reduced (Siqueira et al., 2006).

Immunomoduladory activity

Determined the immunomodulatory activity of six extracts of *C. superba* and *C. rufescens* by *in vitro* assays using murine activated macrophages and lymphocytes. The extracts were obtained from dried stems and leaves of *C. superba* and stalks and leaves of *C. rufescens*. Macrophages were stimulated by IFN-γ and LPS in the presence/absence of the samples, and the production of nitric oxide was measured indirectly by the Griess method. The samples tested did not show a high inhibitory effect on nitric oxide production, where only three of them inhibited this production by about 50%: the extract of *C. superba* and two of *C. rufescens*, however, showed a strong inhibition of lymphocyte proliferation and IL-2 production (Costa et al., 2008). Thus, these results justify the traditional use of some *Cordia* species in the treatment of immune system-mediated pathologies. The immunomodulatory activity of the constituents isolated from the fractions obtained from the methanolic extract of leaves of *C. rothii* was evaluated in an *in vitro* study carried out by Firdous et al. (2014). The results of this study suggested that the compounds isolated could be potential inhibitors of mediators in innate and adaptive immune responses.

Antioxidant activity

A Studied the antioxidant activity of the extract of *C. boissieri* using the DPPH free radical assay. Moderate antioxidant activity was observed on a chromatographic plate, where this species showed small spots or points with low intensity (Salazar-Aranda et al., 2011). Nine compounds from the ethyl acetate fraction of the methanolic extract of *C. sinensis* were isolated and evaluated for antioxidant activity in a study by Al-Musayeib et al. (2011) using the same method. Seven compounds showed significant free radical quenching activity in this assay, and four of these showed a high antioxidant action in comparison with the control substance utilized.

Insecticidal activity

In evaluated the effect of the aqueous extract of *C. verbenacea* on the development of *Spodoptera frugiperda*, examining the variables duration and mortality for the larval and pupal periods, size, weight and presence of morphological alterations of the pupae and fertility of the adults. As a result, the larval state and pupal period of *S. frugiperda* were prolonged, and morphological alterations in the pupae were also observed (Knaak et al., 2012).

Antibiotic-modifying activity

Evaluated the antibiotic-modifying effect of the hexane and methanolic extracts of the leaves of *C. verbenacea* on norfloxacin against *S. aureus*. The extracts at a sub-inhibitory concentration of 32 μg/ml improved the inhibition zone by 50% when combined with the antibiotic compared to the antibiotic alone. That is, the antibiotic activity of norfloxacin was enhanced in the presence of the extracts of *C. verbenacea*, showing significant synergism (Matias et al., 2013b). Another study utilizing the methanolic extract and the methanolic fraction of the methanolic extract of *C. verbenacea* leaves was conducted to evaluate the drug-modulatory activity of this species. The bacteria utilized were *E. coli*, *S. aureus* and *P. aeruginosa* and the antibiotics were gentamicin, amikacin and neomycin. The extract as well as the fraction potentiated the effect of the antibiotics against all bacteria tested with exception of only the methanolic extract combined with gentamicin against *E. coli* (Matias et al., 2013c).

Antifertility activity

A investigation about effect of the extract obtained from leaves of *C. dichotoma* on reproduction utilizing adult female rats (140–220 g). A potential antiimplantation activity was observed, depending on the dose of extract administered. At a dose of 1000 mg/kg, no implantation sites were observed, but there were some behavioral changes such as general weakness, as noted by slow and uncoordinated movements. At 800 mg/kg, pregnancy was blocked 100% and there were no alterations in behavior (Bhattacharya and Saha, 2013).

Conclusion

This review gathered information on the genus *Cordia*, featuring botanical, ethnopharmacological, phytochemical, pharmacological and toxicological aspects. Studies on the genus *Cordia* describe that the species are distributed in diverse regions of the world and are utilized by traditional populations for the treatment of various maladies such as infections, inflammations and pain. With respect to pharmacological potential, species of the genus *Cordia* have been subjected to antimicrobial, antinociceptive, toxicological, antiinflammatory and antiparasitic tests, among others. Various substances have been identified and isolates from species of the genus *Cordia*, particularly secondary metabolites of the class of terpenoids, flavonoids and tannins, as well as their respective chemical structures.

Authors contributions

EEFM, EFA, MKNS and VRAC collected the reports about the botanical, ethno and pharmacological aspects of this genus; HDMC and JGMC supervised the work, drawn the chemical structures and revised all text.

Conflicts of interest

The authors declare no conflicts of interest.

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