Pharmacognostic Evaluation of Ten Species of Medicinal Importance of *Cecropia*: Current Knowledge and Therapeutic Perspectives#

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ABSTRACT

This work covers a systematic review of literature about the genus *Cecropia* from 1978 to 2020, emphasizing the analysis of 10 of the most relevant species and their associated biological activities. *Cecropia* is a neotropical genus, which comprises about 61 native species in the American continent where it is known to be part of the traditional medicine of numerous countries. Secondary metabolites described for this genus showed an elevated structural and functional diversity, where polyphenols have been the most abundant. Based on this diversity, *Cecropia* phytochemicals represent an important source of potential therapeutic agents yet to be exploited. This review also highlights the effectiveness of combining chemometrics and ultra-performance liquid chromatography-tandem mass spectrometry as a novel approach to successfully single out *Cecropia* species phytochemicals. While the medicinal use of *Cecropia* species is officially recognized in National Pharmacopoeias and Formularies of several Latin American countries, it is important to recognize that these phytomedicines are complex mixtures requiring a thorough understanding of their chemical composition and their correlation with biological activities to guarantee their quality, safety, and efficacy.

Introduction

The genus *Cecropia* Loefl. (Urticaceae), with 61 described species, represents the largest genus of Cecropieae [1]. Also, it is notable for being one of the most morphologically and ecologically diverse genus in the tribe [1]. These generally fast-growing trees are widespread and abundant. They can be found across the tropical and subtropical rainforests from Mexico to South America at elevations below 2600 m [2]. *Cecropia* trees are known vernacularly as "guarumo", "guarumbo", "yarumo", "embaúba", "ambay", "trum-

Dedicated to Professor Arnold Vlietinck on the occasion of his 80th birthday.

* Prof. Dr. Mahabir P. Gupta passed away on December 14, 2020.

pet tree" and "torém" [3–7]. Plants within this genus are fast-growing trees, primary colonizers of deforested areas in the tropics [8], and invasive species in non-native regions [9]. In addition, most species within the genus *Cecropia* are ant-plants or myrmecophytes [10]. They may live in a symbiotic relationship with a colony of symbiotic ants, especially ants of the genus *Azteca* [11]. They possess specialized structures for offering shelter and food to ants in exchange for protection against natural enemies [12, 13].

In several Latin American countries, many species of *Cecropia* have been widely used in traditional medicine as a diuretic, cardiotonic, antioxidant, antitussive, and expectorant, and for the treatment of cough, asthma, hypertension, diabetes, inflammation, anxiety, and depression [4, 14–19]. There are also claims of the efficacy of plant-derived material from *C. glaziovii* Snethl. in wound healing, as an analgesic, and for antimicrobial activities [20].

This work covers a systematic review of the genus *Cecropia* obtained from classic books about traditional medicine, theses, and scientific databases including Pubmed, SciFinder, Scopus, and the Web of Science covering dates from 1978 to 2020.

Special interest has been given to 10 species of *Cecropia: C. glaziovii, C. hispidissima* Cuatrec., *C. hololeuca, C. insignis* Liebm, *C. obtusa* Trécul, *C. obtusifolia, C. pachystachya, C. palmata* Willd., *C. peltata* L., and *C. telenitida* Cuatrec., due to their medicinal importance supported by a large number of phytochemical and pharmacological data, which may promote their use as herbal drugs.

▶ **Table 1** summarizes the ethnomedical information of 14 of the most common species within this genus, which are of both human and veterinary medicinal importance. The most frequently claimed medicinal uses were the treatment of cardiovascular diseases and diabetes, followed by the treatment of respiratory conditions. The most popularly used plant parts were the leaves, while the least used were roots and fruits. Generally, the preparation of these plant extracts mainly used water and, in some cases, alcohol.

Interestingly, *C. glasiovii, C. hololeuca* Miq., *C. obtusefolia* Bertol., and *C. pachystachya* Trécul. have already been recognized by local pharmacies and Ministries of Health as useful options to develop herbal products to benefit public health [4, 21–24].

Classification, Taxonomy and Geographical Distribution of the Genus Cecropia

Historically, the taxonomic classification of *Cecropia* was a subject of debate [11, 25] due to its inclusion in the Moraceae, Urticaceae, and Cecropiaceae families [25–29]. Recently, molecular phylogenetic studies [10, 11, 30–36] positioned this genus in the tribe Cecropieae Dumort. of the Urticaceae family [9]. Cecropieae represents a monophyletic group [10] that includes dioecious trees, shrubs, and hemiepiphytes with spiral phyllotaxis, amplexicaul stipules, a reduced system of clear latex-bearing canals, aerial or stilt roots, terminal inflorescences, and staminate flowers with straight filaments [11]. Currently, this tribe comprises 5 monophyletic genera, *Cecropia, Coussapoa* Aubl., and *Pourouma* Aubl. from Neotropics, and *Musanga* C. Sm. ex R. Br. and *Myrianthus* P. Beauv. from Afrotropics [10, 11].

In general terms, trees of the genus *Cecropia* are distinguished mainly by spathes completely enclosing the flower-bearing parts of the inflorescences, usually hollow stems, peltate blades with patches of dense indumentum (trichilia) producing Müllerian bodies at the base of the petiole, and anthers becoming detached at anthesis [1, 37]. From a taxonomic point of view, this genus is relatively well studied. The most comprehensive taxonomic treatment to date corresponds to the monograph published by Berg and Franco-Rosselli [1], which also includes information on the morphological, anatomical, ecological, and geographical aspects of the genus. **Table S1** (Supporting Information) shows the key morphological characteristics of the *Cecropia* species considered in this review.

One of the main taxonomical issues for this genus that has yet to be clarified is its infrageneric classification. The first attempt to establish an infrageneric classification of this genus was made by Snethlage [38], where 42 species were included in 2 sections, Tomentosae and Atomentosae, based on morphological differences in indumentum on perianths of staminate flowers, the length of filaments, and the length of spikes of staminate and pistillate inflorescences. According to Berg and Franco-Rosselli [1], this classification cannot be applied to all known species (probably because it was made with few specimens); therefore, it cannot be used satisfactorily. However, the authors were unable to establish a new or amended infrageneric classification in *Cecropia*, since insufficient knowledge on morphological differentiation was available. Despite this limitation, Berg and Franco-Rosselli recognized 2 large groups of species: *C. peltata*-group characterized by the presence of peltate stigmas, and the *C. telenitida*-group with the upper leaf surface covered with relatively dense arachnoid indumentum or glabrous, petioles usually lacking a trichilia, and the outer surface of the stipules and spathes are either glabrous or villous with long, nearly soft, whitish hairs. Recent molecular work showed *C. sciadophylla* Mart. (non-myrmecophytic species) as sister to the remaining studied taxa, followed by *C. hololeuca*, also, a polytomy that includes *C. hispidissima* Cuatrec. and *C. litoralis* Snethl. as well as all remaining species embedded in the *Cecropia* clade I (most species with *Azteca* mutualism) and *Cecropia* clade II (a group of mostly non-myrmecophytes) [10].

Another taxonomic problem pending to be resolved is the delimitation of *Cecropia* species that have a wide geographical distribution and high morphological variations, some of which form a complex of species, such as *C. angustifolia* Trécul, *C. membranacea* Trécul, *C. obtusifolia* Bertol., *C. peltata* L., *C. pachystachya* Trécul, *C. latiloba* Miq., *C. sciadophylla*, and many cryptic members of the *Cecropia telenitida*-group with restricted distribution [1]. A species complex occurs when there is a high morphological variation within a taxon, but there is not sufficient evidence to delimit the individual species, so all potential entities can be labeled morphotype or subspecies [39, 40]. Recently, notable morphological and chemical differences were found in the 2 morphotypes described in *C. obtusifolia*, suggesting that these 2 groups may deserve a different taxonomic recognition [41]. Moreover, Santos et al. [42], through morphological and molecular data, showed major differences between *C. pachystachya* synonymized morphotypes, which raises the need for a taxonomic and nomenclatural revision of the *C. pachystachya* complex and subsequent reestablishment of at least 4 synonymized taxa (i.e., *C. adenopus* Mart. ex Miq., *C. digitata* Klotzsch, *C. lyratiloba* Miq., and *C. catarinensis* Cuatrec).

▶ **Table 1** Ethnomedical uses of *Cecropia* species.

Species name	Common name	Plant part used	Use	Country	Reference
C. ficifolia Warb. ex Snethl.	Bocono/Tiopi; Ambaibo	Bark	VET: vomit, scabies	Bolivia	[127]
C. glaziovii	Embauba-vermelha	Leaves	Heart, inflammatory and respiratory conditions, diabetes, hypertension, cough, and bronchitis	Brazil	[20, 86, 96]
C. hispidissima	Bocino	n. s.	Skin diseases	Ecuador	[128]
C. hololeuca	Emabaúba, Imbaúba, Embaúba branca, Embaúba prateada, Trumpet tree, silver embauva, black embauva, white embauva	Leaves, fruits, and sprouts	Diuretic, diabetes, hypertension, sedative, refreshing, inflammation, thoracic, healing, expectorant, asthma, cough, suppressant, resolutive, antithermal, adjuvant in malaria, cancerous tumors	Brazil	[6, 90, 129, 130]
		Roots and/or leaves	Diabetes, diuretic (oral administration), furunculosis (external use)	Brazil	[130]
C. insignis	Guarumo, chancarro, jaruba, yagruma, trumpet tree	Leaves	Diuretic, hypertension, asthma, bronchitis, and inflammation	Mexico	[131, 132]
C. mutisiana Mildbr.	Agrumo, calentano, guarumo, orumo, yarumo	Roots, leaves, and bark	Mild respiratory diseases, cough, asthma, liver diseases, diabetes, an anti-inflammatory, infections, scar formation, sunburns, chorea, cardiac toner, heart hypertrophy, diuretic, hypertension	Colombia	[133]
C. obtusa	Imbaúba; Embaúba	Leaves	Diabetes, leishmaniasis	Brazil	[130]
	Cetico blanco	Bark	Kidney, prostate problems	Peru	[134]
C. obtusifolia	Guarumbo, Chancarro, Hormiguillo, Chiflon and Koochl'e	Leaves	Asthma, cough, bronchitis, fever, hepatic and kidney diseases, rheumatism, inflammation, obesity, heart disease, hypertension, diuretic, nervousness, bradycardia, dropsy, diabetes type 2, wounds, ant and scorpion stings	Mexico	[23, 59, 80, 113, 135]
		Leaves, stem, bark, and root	Diabetes type 2	Mexico	[23, 79, 81, 135]
	Guarumo	Leaves and stems	Cardiovascular diseases	Panama	[14]
	Grayumbo, Trompeto, Guarumo, Yagrumo, Guarumbo, Hormiguillo and Chancarro	Leaves	Sedative, arthritis and rheumatism	El Salvador	[113]
	Guarumbo	Sap	Warts	Mexico	[136]
C. pachystachya	Embaúba-prateada, Embaúba, Ambay	Leaves, bark	Antitussive, expectorant, asthma, diuretic and hypoglycemic agent, inflammation, wound healing, hypertension, cardiac diseases, and as antipyretic for the treatment of fever in malaria	Brazil	[15, 90, 107]
		Powder fruit	Bronchitis	Brazil	[137]
	Embauba, vermelha	Leaves	Skin irritation and verminosis	Brazil	[138]
	Embauba	Leaves	Hypertension, leukemia, pneumonia, kidney disease, and cough	Brazil	[139]
C. palmata	Torém, imbaúba	Leaves	Stimulant, tonic, and diuretic	Brazil	[130]
	embaúba-vermelha	n. s.	Rheumatism, inflammation, antioxidant, antitumor, act in the central nervous system, anxiolytic and antidepressant, asthma, hypertension, diabetes type 2	Brazil	[45]
		Leaf/bark/stem	Coronary heart disease, rheumatism, and tranquilizer	Brazil	[140]

continued

▶ **Table 1** *Continued*

Species name	Common name	Plant part used	Use	Country	Reference
C. peltata	Bois canôt	Leaves	Hypertension, fever, common cold and cough, diabetes, rheumatism, VET: skin conditions, anhydrosis, kidney problem, respiratory conditions in horses	Trinidad and Tobago, and British Columbia	[141–144]
		Roots	VET: snakebite	Trinidad	[143]
		Ridges from inside stem	Carminative	Trinidad and Tobago	[141]
		Leaves	Aches, abscesses, coughs, pains, fever, pertussis, pharyngitis, gingivitis, bronchitis, skin lesions, antiparasitic agent, digestive problems, antibilious, cardiotonic, diuretic agent, against blennorrhea and warts	Nicaragua, Jamaica, Guatemala, Colombia	[97, 109, 145–148]
	Imbaúba, simbaúba		Heart diseases and diabetes.	Brazil	[130]
	Guarumo/Yarumo		Asthma, bronchitis, lung diseases, blood and circulatory system, heart diseases, gallbladder, sunstroke, diuretic, cardiovascular, metabolic, and respiratory disorders, for their wound-healing and diuretic, diabetes mellitus, heart diseases and hypertension, sedative and antimicrobial agent, albuminuria, kidney infections, heart conditions and nervous diseases, and to promote good kidney function	Colombia	[5, 59, 70, 77, 80, 109, 130, 141, 149, 150]
C. schrebiana Miq.	Yagruma	Leaves	Asthma, anticatarrhal, cardiotonic	Cuba	[151, 152]
C. sciadophylla	Bocobí; hierba de loro		VET: Respiratory system (cold and flu)	Bolivia	[127]
C. telenitida	Guarumo; guarumbo; yarumo plateado; yarumo blanco		Inflammation	Colombia	[7, 153]

n. s. = not specified; VET: veterinary use

Phytochemistry

Extraction and methods of analysis

Most studies on *Cecropia* have mainly focused on the polar constituents found in its leaves. Water and hydroalcoholic mixtures (H_2O : EtOH or H_2O : MeOH), commonly chosen as extraction solvents, are described as the most appropriate systems for polyphenol extraction. Nevertheless, other solvents such as butanol and ethylacetate (EtOAc) have been also utilized.

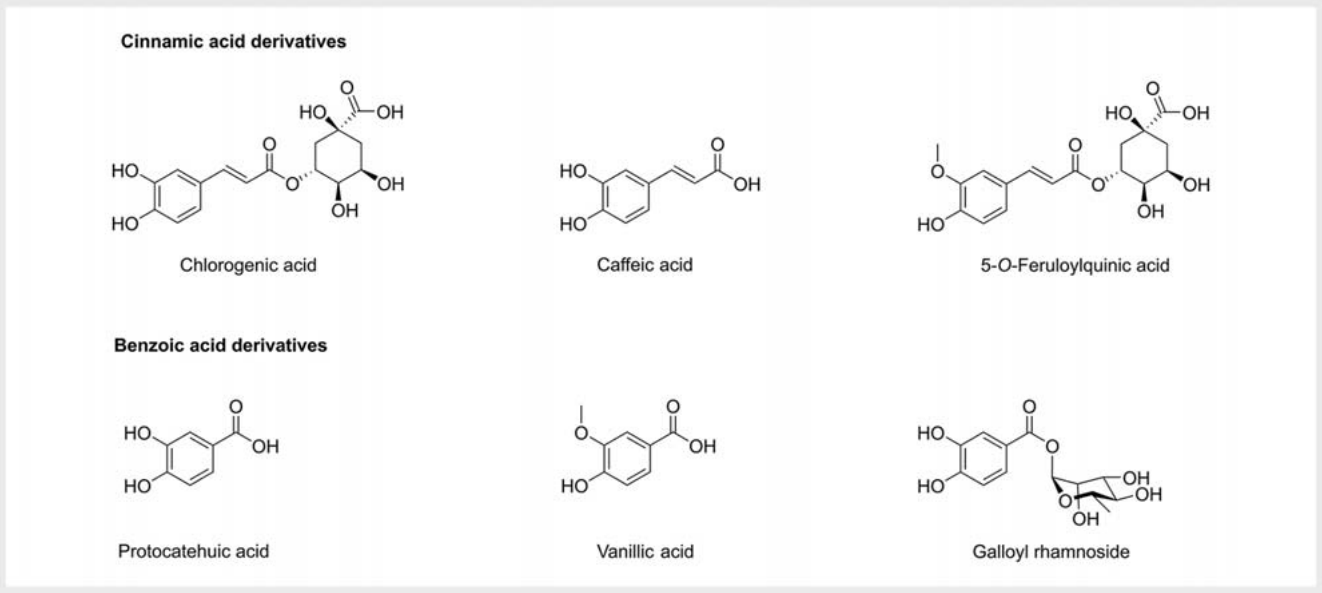
Among the extraction methods, the most frequently used were maceration, infusion, decoction, Soxhlet extraction, and ultrasound-assisted extraction. Optimal extraction methods have been evaluated by only a few studies [43, 44], where the best extraction parameters were estimated by statistical approaches to reduce the number of experiments and to investigate the effects of various factors, such as temperature, extraction time, and solvent concentration. According to these investigations, extracts with 70% and 80% ethanol (EtOH) presented a higher chlorogenic acid, total flavonoid, and flavonolignans content, while extracts with 20% EtOH showed a higher caffeic acid concentration.

High-performance liquid chromatography coupled to a diode array detector (HPLC–DAD) was the most common analytical technique used to identify and quantify the secondary metabolites in these extracts by a targeted approach (**Table 2S**, Supporting Information). The identity of polyphenols is usually confirmed by comparison with both the retention time and UV spectrum of authentic standards.

Interestingly, liquid chromatography coupled with mass spectrometry (such as UPLC-MS/MS) has been established as a powerful technique for rapid analysis of nonvolatile compounds found in *Cecropia*, and electrospray ionization in positive and negative ion mode has been identified as the most useful ionization technique. Additionally, identification of compounds was based on different levels of confirmation: structure confirmed by comparison with authentic standards, possible structure by library spectrum match, and proposed candidates based on MS^2 experimental data.

Full identification of the chemical structure of novel compounds found in *Cecropia* was performed by NMR spectroscopy: yarumic acid (*C. telenitida*), isoyarumic acid (*C. telenitida*), *ent*-mururin A (*C. obtusifolia*), and *ent*-mururin B (*C. obtusifolia*).

Extensive research has been focused on the phenolic compounds of polar extracts, while fewer phytochemical studies have included nonpolar constituents of *Cecropia* leaves. Schmidt et al. [45] showed, by HPLC-DAD (210 nm) and UHPLC-MS/MS analysis, that EtOAc was more efficient extracting triterpenes from *C. obtu-*



▶ **Fig. 1** Chemical structures of main phenolic acids reported for plants of the genus *Cecropia*.

sa and *C. palmata* than chloroform. Additionally, Guerrero et al. [46] used GC-MS analyses to show the presence of phenolic acids (vanillic acid), tetracyclic triterpenoids (stigmast-4-en-3-one, 4-cholestene-3,24-dione, 4,22-cholestadien-3-one), fatty acids (palmitic acid, stearic acid), and other nonpolar compounds such as 4-vinyl-2-methoxy-phenol, 2-methylbenzaldehyde, 2,3-dihydrobenzofuran, and 3′-methoxyacetophenone, in the dichloromethane extract of *C. obtusifolia* leaves.

Chemical Constituents

Available literature describes the phytochemistry of the genus *Cecropia* consisting of almost 100 identified compounds, which include phenolic compounds, particularly phenolic acids, flavonoids, condensed tannins, triterpenoids [7,47,48], flavonolignans, and iridoids [49]. Names and source of these constituents are listed in **Table 2S** (Supporting Information) and their structures in ▶ **Figs. 1**–**3**.

Phenolic acids

Phenolic constituents dominate the chemistry of *Cecropia*, being one of the most studied constituents in this genus. Several phytochemical investigations have revealed the presence of cinnamic acid derivatives (chlorogenic acid, caffeic acid, sinapic acid hexoside, and 5-*O*-feruloylquinic acid) and benzoic acid derivatives (protocatehuic acid, vanillic acid, and galloyl acid derivatives) (▶ **Fig. 1**).

Chlorogenic acid, the ester of caffeic acid with quinic acid, is the main phenolic acid found in all *Cecropia* species, reaching a concentration of up to 28 mg/g of aqueous leaf extract in *C. pachystachya* (**Table 2S**, Supporting Information). Due to its good chemical stability, pharmacological relevance, and relatively high concentration, chlorogenic acid has been selected as an appropriate chemical marker for the chemical standardization and quality evaluation of *Cecropia* products [50].

Flavonoids

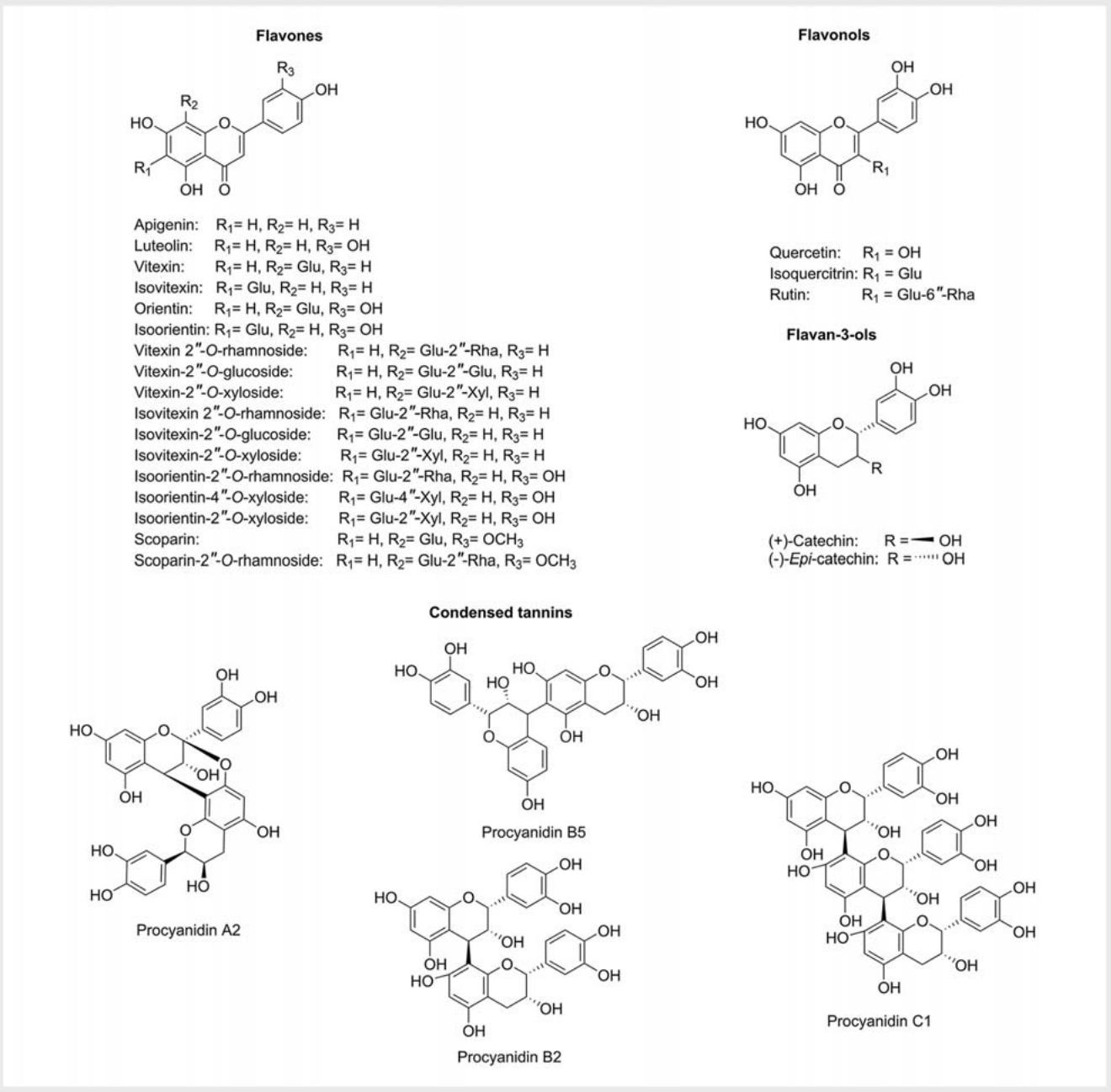
Flavonoids constitute another important group of compounds observed in *Cecropia* species (**Table 2S**, Supporting Information and ▶ **Fig. 2**), which are found in relatively high concentrations [44, 49,51,52]. Many studies have associated flavonoids with the biological and pharmacological effects described for *Cecropia* [4]. Among the broad variety of flavonoids detected, the majority belonged to the flavone or flavonol classes, with luteolin, apigenin, or quercetin being the main aglycones.

Within this class, flavones derived from the aglycones luteolin and apigenin were the main subclass of flavonoids present in *Cecropia*, predominantly in the form of monoglycosides and diglycosides with different sugar units, such as hexoses, pentoses, and deoxyhexoses. Among flavone glycosides, *C*-linked monoglycosyl flavones, such as isoorientin, orientin, isovitexin, and vitexin were the most abundant, with isoorientin being the main constituent in *C. glaziovii, C. hololeuca, C. insignis, C. obtusifolia, C. pachystachya,* and *C. peltata* [16,41,44,49,52–54]. The occurrence of di-*C,O*-glycoside flavones was also described [44,49,54].

It is noteworthy that the diversity of flavones glycosides observed in *Cecropia* was strictly due to differences in sugar units and types of glycosidic bonds, while aglycones remained similar for almost all species [49].

Other minor flavonoids found in *C. hololeuca, C. insignis, C. obtusifolia, C. pachystachya,* and *C. peltata* included methylated derivatives, such as scoparin (diosmetin-8-*C*-hexoside) and scoparin-2″-*O*-rhamnoside [49,54].

Regarding the effect of seasonal variation on flavonoid content, Rivera-Mondragón et al. [44] showed that there was no clear correlation of those variables in *C. insignis, C. hispidissima C. obtusifolia,* and *C. peltata*, collected in Panama. Similar findings were described by Costa et al. [55], where no correlation was found between pluviosity and the production of *C*-glycosylflavonoids in *C. glaziovii* collected in Brazil. In contrast, Luengas-Caicedo et al.



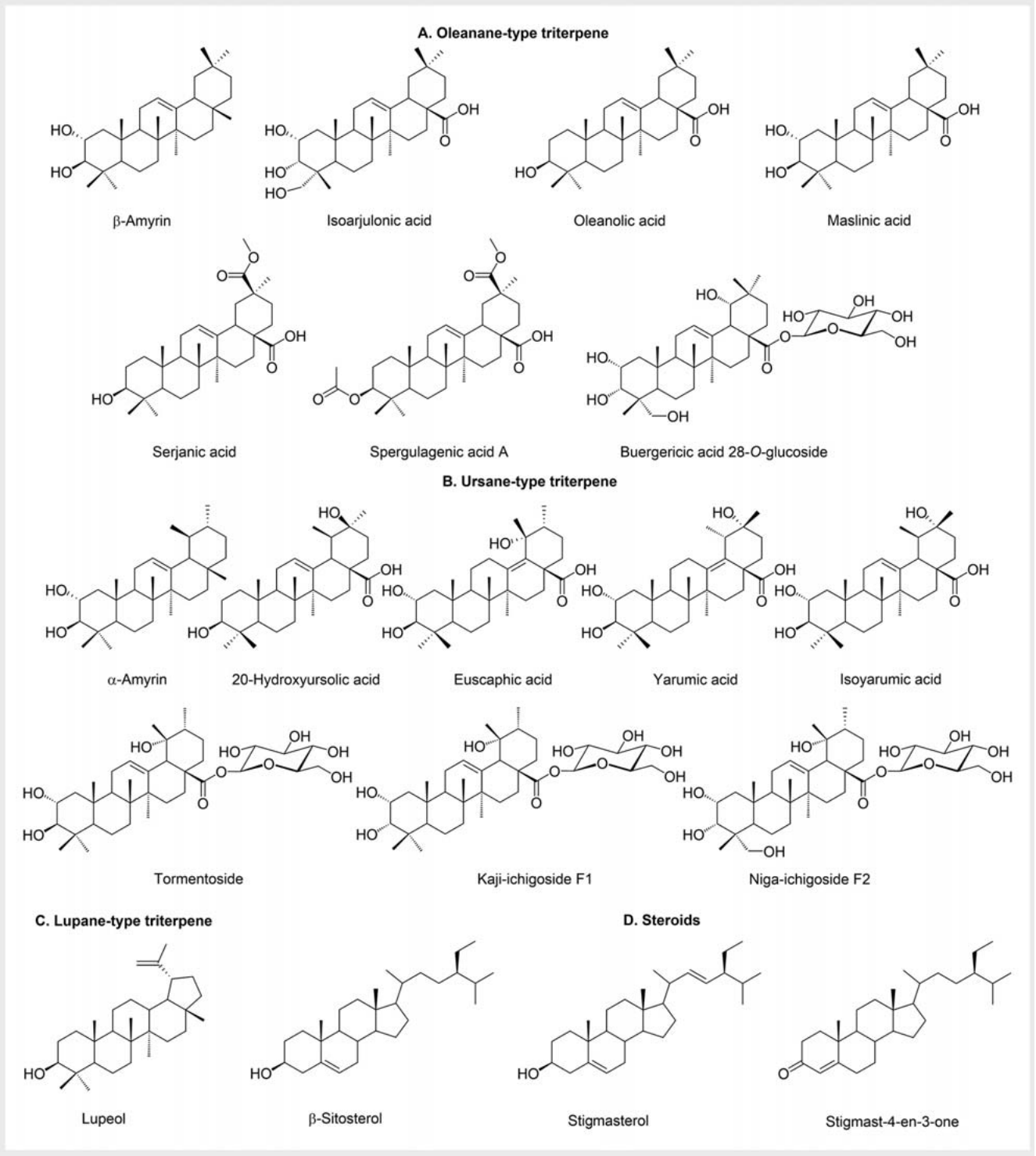
▶ **Fig. 2** Chemical structures of main flavonoids reported for plants of the genus *Cecropia*.

[3] found a higher flavonoid content in *C. glaziovii* leaf extracts collected in Brazil during the dry season compared to those collected during the rainy period.

The presence of flavonols in the genus *Cecropia* was remarkable. Within this sub-class of flavonoids, quercetin, rutin, and isoquercitrin were predominant in some *Cecropia* species [15, 44, 49, 54, 56–58] (**Table 2S**, Supporting Information). Other flavonol *O*-glycosides, like quercetin 3-*O*-hexoside, isorhamnetin-3-*O*-hexoside, and isorhamnetin-3-*O*-rutinoside, have also been characterized in *C. hololeuca* [49] (**Table 3S**, Supporting Information), while flavan-3-ols such as (+)-catechin and (−)-epicatechin have been found in the aqueous, methanolic, or ethanolic extracts of *C. pachystachya, C. glazoivii*, and *C. hololeuca* leaves [15, 20, 21, 49, 56].

Condensed tannins

All condensed tannins found in the *Cecropia* species belonged to the procyanidin family, consisting of oligomers or polymers of catechin, epicatechin, and/or gallocatechin. Procyanidin A2, B2, B5, and C1 were reported in both free and glycosidic forms (**Table 2S**, Supporting Information and ▶ **Fig. 2**). These compounds have been mainly identified in species from South America: *C. pachystachya, C. glaziovii,* and *C. hololeuca*. Catechin and epicatechin, the



▶ **Fig. 3** Chemical structures of main terpenoids reported for plants of the genus *Cecropia*.

precursor of procyanidins, were also frequently detected in different extracts of this plant.

Pentacyclic triterpenoids and steroids

Interestingly, *Cecropia* plants are also a rich source of triterpenes and steroids (**Table 2S**, Supporting Information and ▶ **Fig. 3**). The main triterpenoid skeletons found in *Cecropia* belonged to the pentacyclic oleanane-, ursane- and lupane groups. Several pentacyclic terpenoids found in roots were aglycones. Yarumic acid, isoyarumic acid, serjanic acid, spergulagenic acid A, 20-hydroxy-ursolic acid, and goreishic acid I were obtained from the dichloromethane and EtOAc extracts of the root of *C. telenitida*

[7, 47, 48]. Moreover, hydroalcoholic leaf extracts were rich in saponins (triterpenoid glycosides), having glucose moieties located predominantly at the C-28 position. Rivera-Mondragon et al. reported the presence of niga-ichigoside F2, kaji-ichigoside F1, tormentoside, and buergericic acid 28-*O*-glucoside in *C. obtusifolia, C. peltata, C. insignis,* and *C. hispidissima* [54], while Schmidt et al. [45] identified lupeol, α-amyrin, β-amyrin, oleanolic acid, and maslinic acid in *C. obtusa* and *C. palmata*.

Steroids such as stigmasterol, sitosterol, stigmast-4-en-3-one, 4-cholesten-3,24-dione, and 4,22-cholestadien-3-one have also been described [45, 46, 59, 60].

Table 2S (Supporting Information) shows the most important triterpenoids and steroids identified in *Cecropia*. No essential oils have been described for this genus in the literature consulted for the present review.

Other constituents

While most phytochemical studies focused on identifying and isolating flavonoids, other components that have gained less attention are worth mentioning in this review. For instance, the iridoids geniposide 1 and 2 were found in the leaves of *C. pachystachya* and *C. hololeuca* [49] and the flavonolignans *ent*-mururin A and *ent*-vaccinin A in the leaves of *C. obtusifolia* [61]; the coumarins 4-ethyl-5-(n-3valeroil)-6-hexahy-drocoumarin, scopoletin [4, 59], some organic acids, anthraquinones, and 1 alkaloid were also found in *Cecropia* species (**Table 4S**, Supporting Information) [59, 62, 63].

Metabolomics Approach

Recently, metabolomic approaches such as LC-HRMS, mainly through untargeted data-dependent MS/MS methods, have provided new standpoints to help the chemical profiling and fingerprinting of several medicinal plants. Untargeted metabolomics in combination with chemometrics analysis is a powerful approach for detecting as many metabolites as possible and provides an appropriate platform for comparing and revealing important differences among plant species.

Significant efforts have been carried out by applying this approach to *Cecropia* species. For instance, tentative identification of 37 compounds in *C. pachystachya* and *C. hololeuca*, including flavonoids, phenolic acids, flavan-3-ols, condensed tannins (procyanidins), and iridoids, was carried out through UV analysis and MS/MS [49]. This study showed that *C. pachystachya* produced a higher diversity of flavones than *C. hololeuca* and that orientin and isoorientin were the major flavones in both plant species. Similarly, high-performance liquid chromatography-diode array detection-quadrupole time of flight-tandem high-resolution mass spectrometry (HPLC-DAD-QTOF) in positive and negative ionization mode identified 47 chemical constituents in the leaves of 6 *Cecropia* species [41, 54]. These compounds included 2 phenolic acids, 33 flavonoids, 3 flavonolignans, and 9 saponins, many of which were found to be unknown for these species. Chemometric analysis, such as hierarchical cluster analysis and principal component analysis, revealed that the most abundant flavonoids detected in *C. angustifolia, C. insignis, C. obtusifolia, C. peltata*, and *C. telenitida* were flavone *C*-glycosides. Interestingly, *C. hispidissima* was the most segregated species, due to its high relative concentration of flavonol mono- and diglycosides. Additional findings showed that *C. obtusifolia* "burriada-type" and "obtusifolia-type" belonged to different clusters, proposing an inaccurate taxonomic classification of these species [41]. This study also showed that the chemical profile of the leaf of *C. obtusifolia* "burriada- type" was the most diverse of all studied species, while *C. telenitida* showed the lowest diversity.

Pharmacological Effects

Numerous studies highlighting the pharmacological properties of different extracts of *Cecropia* species are summarized *vide infra* in this review.

Antioxidant Effect and Skin Protection

While the antioxidant capacity of the genus *Cecropia* has been widely studied, its wound healing and skin protection potential have only been recently studied. More than 50% free radical scavenging capacity was observed when an aqueous extract of *C. hololeuca* bark [64] and a methanolic [16, 65] extract and hydroethanolic and ethanolic [66] extracts of *C. pachystachya* leaves were tested in different antioxidant models, such as phosphomolybdenum, 1,1-diphenyl-2-picrylhydrazine, carotene/linoleic acid bleaching, and thiobarbituric acid reactive substances (**Table 5S**, Supporting Information).

Additionally, both an ethanolic and a hydroethanolic extract of *C. pachystachya* prevented the production of advanced glycation end products (**Table 5S**, Supporting Information) and were able to stimulate fibroblasts proliferation *in vitro*, with no sign of cytotoxicity [66].

Collagenase levels and elastase activity were reduced by a hydroethanolic extract of *C. pachystachya* [66], while an ethanolic extract of the leaves of *C. obtusa* decreased collagenase and protein carbonyl levels [67]. Chlorogenic acid, the main component of *C. obtuse*, was also capable of increasing collagen and hyaluronic acid contents. Furthermore, *C. obtusa* extract prevented the formation of UV-induced pro-inflammatory cytokines IL-1β and IL-6 in HaCaT keratinocytes [67] (**Table 5S**, Supporting Information), protected keratinocytes from UVA-induced damage, and absorbed UVA/UVB radiation, while showing a good radical scavenging capacity (**Table 5S**, Supporting Information) [68].

Gels containing 2% and 5% of an ethyl acetate extract of *C. pachystachya* promoted the healing process in rats, causing less neovascularization and cellularity, better tissue repair, and younger and more homogeneous tissue when compared to the control. These effects, together with the antioxidant properties shown by this extract (**Table 5S**, Supporting Information), propose a further evaluation of this plant as a topical treatment in the management of skin lesions [69].

In the same line, the aqueous and ethanol extracts of *C. peltata* significantly reduced injured areas in animals (**Table 5S**, Supporting Information) and showed clean wounds with healthy granulation tissue. In all groups treated, an increase in protein content, hydroxyproline, and hexosamine was observed, as well as a better lay-down of collagen when compared to respective controls [70].

Hypoglycemic Effect and Anti-diabetic Potential

Available literature showed that polar extracts of the leaves of *C. glaziovii, C. obtusifilia, C. pachystachia,* and *C. peltata* had a hypoglycemic effect in different animal models.

Thus, a standardized hydroalcoholic extract of *C. glaziovii* showed antihyperglycemic activity and improved glucose tolerance in diabetic rats [71]; aqueous and butanol extracts of *C. obtusifolia* significantly reduced blood glucose levels in normal and pancreatectomized dogs [72], diabetic rats [73], diabetic mice [74], and hyperglycemic rabbits [75, 76], and its methanol extract reduced plasma glucose in healthy mice [77] (**Table 5S**, Supporting Information). Interestingly, the hypoglycemia observed by the aqueous extract of *C. obtusifolia* was not accompanied by a rise in plasmatic insulin, suggesting that this effect was unrelated to beta-pancreatic cell stimuli [72]. These extracts showed similar hypoglycemic effects to 3 mg/kg glibenclamide. Isoorientin and chlorogenic acid, the main constituents of these extracts, were proposed as responsible agents of the hypoglycemic effects of both extracts [73, 78, 79]. Isoorientin reverted TNF-α-induced insulin resistance in adipocytes, activating the insulin signaling pathway [79], and showed a strong antioxidant effect that may also contribute to the hypoglycemic effect of chlorogenic acid [59].

Moreover, a butanol extract of *C. obtusifolia* inhibited gluconeogenesis in diabetic rats [75, 79] and α-glycosidase activity *in vitro* [78] and reduced glucose-6-phosphatase activity in rat liver microsomes [80] (**Table 5S**, Supporting Information).

Clinical studies carried out for *C. obtusifolia* aqueous extract showed a noteworthy and sustained hypoglycemic effect in type 2 diabetic patients after 32 weeks of treatment (**Table 5S**, Supporting Information). Glycosylated hemoglobin reduction was also seen after 6 weeks of administration of this extract (**Table 5S**, Supporting Information), with no significant changes in insulin secretion, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels, indicative of no hepatotoxicity [81]. In another study, this extract administered with glibenclamide produced a considerable hypoglycemic effect and was effective in reducing fasting blood glucose (**Table 5S**, Supporting Information) [82]. Furthermore, isoorientin decreased circulating radical scavengers in diabetic patients and reduced symptoms of associated complications [59]. Altogether, these findings promote the development of *C. obtusifolia* as an antidiabetic agent [83].

Similar to *C. obtusifolia*, a butanol and an aqueous extract of *C. peltata* prevented the rise of plasma glucose and inhibited gluconeogenesis [80, 84] and glucose-6-phosphatase activity [80]. In addition, methanol extracts of *C. peltata* and *C. pachystachya*, mainly constituted by chlorogenic acid and isoorientin [84], produced hypoglycemia in diabetic rats [65, 77] (**Table 5S**, Supporting Information).

Cardiovascular Effect

Extracts of the leaves of 3 species of *Cecropia*, namely *C. glaziovii, C. obtusifolia,* and *C. pachystachya*, were studied for their hypotensive effect on both hypertensive and normotensive rodent models.

Oral administration of aqueous and butanol extracts of *C. glaziovii*, as well as intravenous administration of *C. glaziovii* (butanol) [85, 86] and *C. obtusifolia* (aqueous and ethanol), produced hypotension [87–89]. These studies suggested that the effect caused by the butanol extract of *C. glaziovii* was mediated by the renin-angiotensin system [86], while hypotension induced by its aqueous extract was independent of the inhibition of the angiotensin-converting enzyme (ACE) (**Table 5S**, Supporting Information) [87].

Vasodilation produced by a methanol extract and a flavonoid containing a fraction of *C. lyratiloba* was endothelin dependent, possibly by stimulation of NO production. Interestingly, while the crude extract was active, its main flavonoids isoorientin and a mixture of orientin/isovitexin were inactive when individually tested [90]. Furthermore, this flavonoid-containing fraction induced cardiac depression and inhibited adrenaline-induced contractions in aortic rings (**Table 5S**, Supporting Information) [90, 91]. Similarly, a standardized hydroalcoholic extract of *C. glaziovii* caused ring aorta relaxation (**Table 5S**, Supporting Information) [71], as well as its butanol fraction. The latest fraction also blocked the peak Ca^{++} current in chromaffin cells of a PC12 cell line [85].

The aqueous extract of *C. pachystachya* caused hypotension and tachycardia [24], possibly due to the central blockage of sympathetic nerves of vessels and central cholinergic inhibition of the heart. It was also suggested that its cardiotonic effect may be due to inhibition of the Na/K pump [92]. In addition, *C. pachystachya* also reduced inflammation and renal lesions associated with ACE-inhibition, reduction of macrophage infiltration, angiotensin II and c-Jun *N*-terminal kinase expression, and arginase activity in the renal cortex of rats (**Table 5S**, Supporting Information) [93, 94]. Also, the aqueous extract of the leaves of *C. peltata* showed a positive inotropic effect on isolated guinea pig atria and caused injury to cardiomyocytes [95].

To understand the mechanisms by which these extracts and their constituents may interact with the cardiovascular system, additional *in vitro* studies were carried out and their findings summarized below.

A methanol fraction of the spitules of *C. glaziovii* almost completely inhibited ACE activity, while a similar type of extract of its leaves showed half of this effect [58]. The ethanol extract of *C. hololeuca* also inhibited ACE activity (**Table 5S**, Supporting Information). The major components within these active extracts were identified as orientin, isoorientin, (+)-catechin, (−)-epicatechin, and 2 (−)-epicatechin-derived oligomeric procyanidin B2, procyanidin C1, and chlorogenic and protocatechuic acids [58]. Interestingly, while these compounds showed little activity when tested individually, the fraction containing mainly procyanidins showed almost a complete inhibition of ACE activity at the same concentration [58].

Moreover, a radioligand-binding-based *in vitro* study was used to test the methanol/dichloromethane (1 : 1) and the ethanol extracts of the stems and leaves of *C. obtusifolia.* The results showed that both extracts inhibited angiotensin II binding to the angiotensin II type 1 receptor and BQ-123 binding to the endothelin-1

type A receptor in more than 50% of the control (**Table 5S**, Supporting Information) [14].

Anti-inflammatory Effect

Different plant parts of only 4 *Cecropia* species have been studied for their anti-inflammatory properties.

Thus, aqueous extract of the leaves of *C. glaziovii* reduced proinflammatory cytokines, cell infiltrates, myeloperoxidase activity, nitrite/nitrate concentration, lactate dehydrogenase activity, and total protein levels with concomitant attenuation of all parameters associated with oxidative damage caused by carrageenin. Chlorogenic acid, isoorientin, and isovitexin were identified as the major compounds of this active extract [96].

The aqueous extract of the bark of *C. hololeuca* reduced mouse paw edema and decreased the production of nitric oxide, tumor necrosis factor-alpha (TNF-α), and interleukin-1-beta (IL-1β) on murine macrophages J774A.1 cells (**Table 5S**, Supporting Information), without signs of cytotoxicity [64].

Nonpolar extracts of the leaves of *C. pachystachya*, like hexane and dichloromethane, and 2 of its main constituents, β-sitosterol [97] and pomolic acid, reduced the inflammatory response in carrageenan-induced mouse paw edema. Moreover, pomolic acid reduced the *in vivo* production of IL-1β by hindering the viability of neutrophils through apoptosis. Trans-phytol, α-amyrin, and ursolic acid, identified also in the dichloromethane extract, showed anti-inflammatory effects as well (**Table 5S**, Supporting Information) [60]. Besides, its methanolic extract showed acute and topical anti-inflammatory properties in ear edema (**Table 5S**, Supporting Information) [16, 98] and a moderate chronic skin anti-inflammatory effect with a decrease in vasodilation, edema, cell infiltration, and epidermal hyperproliferation [16].

Lastly, in the roots of *C. telenitida* a couple of pentacyclic triterpenes, namely serjanic acid and spergulagenic acid A, blocked the secretion of proinflammatory cytokines (IL-1β, IL-12p40, IL-12p70, TNF-α) in a dendritic cell-based assay. Moreover, spergulagenic acid A also inhibited nitric oxide production in lipopolysaccharide-stimulated dendritic cells [7].

Central Nervous System Effects

The butanol fraction of *C. peltata,* rich in flavonoids, showed anticonvulsant, anxiolytic, and sedative effects in mice at 80 mg/kg. These effects were greater than ethanolic, aqueous, and hexane fractions [5, 99].

An antidepressant effect was caused by the aqueous extract of the leaves of *C. glaziovii* and its butanol fraction. The results proposed that this effect may be due to the blockade of monoamine uptake, mainly the uptake of [3H]-noradrenaline. Biochemical analysis of the animals treated with the flavonoids containing fraction showed a significant increase in monoamines levels in the hippocampus (**Table 5S**, Supporting Information) [100].

In addition to that, an antidepressant effect was also seen by oral administration of an enriched *C*-glycosyl flavonoid fraction and an aqueous extract obtained from leaves of *C. pachystachya* [15, 101]. These extracts prevented both behavioral (hyperlocomotion) and pro-oxidant effects (an increase of lipid peroxidation and carbonyl protein formation, and a decrease in total thiol content) of ketamine in a rat model of mania. These effects were thought to be mediated by chlorogenic acid, orientin, isoorientin, isovitexin, and isoquercitrin present in both extracts [57]. The sedative effect produced by *C. pachystachya* aqueous extract (180–600 mg/kg) was comparable to diazepam 10 mg/kg [92].

C. pachystachia was also studied for its antinociceptive effect. A methanol extract of its leaves was effective, in a dose-dependent manner, against pain induced by acetic acid and on the second phase of the formalin test (**Table 5S**, Supporting Information) [98].

Other Biological Effects

Extracts of *C. glaziovii, C. obtusifolia, C. pachystachya,* and *C. peltata* have been also studied for additional biological activities, namely, antihistamine-induced bronchospasm, cytotoxicity, antimicrobial, gastric mucosal protection, and genotoxicity.

Administration of a standardized aqueous extract, as well as a procyanidin/flavonoids- enriched butanol fraction of the leaves of *C. glaziovii*, showed protection against histamine-induced bronchospasm in guinea pigs. Moreover, *in vitro* incubation of a flavonoid enriched butanol fraction decreased the maximal response of tracheal muscle to histamine without modifying the EC_{50}, suggesting a noncompetitive inhibitory effect of *C. glaziovii* to histamine (**Table 5S**, Supporting Information). Bronchodilation caused by this extract appeared to be related to β-adrenergic activity since this effect was prevented by pretreatment with propranolol [102].

A methanol extract of the leaves of *C. pachystachya* significantly diminished the viability of human promyelocytic leukemia cells expressing Bcl-2 and human immortalized line of T lymphocyte (Jurkat cells) (**Table 5S**, Supporting Information) in a study proposing the capacity of the extract to overcome resistance due to its ability to downregulate the anti-apoptotic oncoprotein Bcl2 [98]. Another study carried out on human prostate adenocarcinoma cells showed the capacity of its triterpene-enriched fraction to reduce the number of viable cells by senescence induction (**Table 5S**, Supporting Information) [103]. Furthermore, the triterpenes tormentic, 2-α-acetyl tormentic, 3-β-acetyl tormentic, and euscaphic acids, obtained from the dichloromethane fraction of a methanol extract of *C. lyratiloba* roots, were cytotoxic against sensitive and multidrug-resistant leukemia cell lines (**Table 5S**, Supporting Information) [104–106]. These findings emphasize the potential of some species of *Cecropia* to be further studied as anticancer agents.

Other studies also evaluated the antiparasitic and antibiotic properties. Thus, ethanol extracts of woods, roots, and leaves, as well as a hexane extract of the roots of *C. pachystacya*, showed a reduction in the parasitemia of malaria-infected mice (**Table 5S**, Supporting Information) [107], while chlorogenic acid, catechin, epicatechin, isoquercitrin, and orientin (from the ethyl acetate fraction of its leaves) inhibited *Leishmania (L.) amazonensis* promastigotes arginase activity (**Table 5S**, Supporting Information) [56]. Moreover, orientin, isoorientin, vitexin, isovitexin, rutin, and chlorogenic acid obtained from this plant were described as quorum sensing (QS) inhibitors using *Chromobacterium violaceum* (in-

hibition of violacein pigment) and *Escherichia coli* (bioluminescent inhibition) as biosensors in the agar diffusion tests (**Table 5S**, Supporting Information) [108]. Similarly, the ethanolic extract of *C. peltata* was studied for its antimicrobial effect and shown to be active against *Staphylococcus aureus, Bacillus cereus*, and *E. coli* (**Table 5S**, Supporting Information) [109].

Further studies about the biological effects of *C. glaziovii* extracts showed that the ethanol extract of its leaves reduced liver injury and was active against *Herpes simplex* virus type 1 (acyclovir-resistant strain) (**Table 5S**, Supporting Information) [110]. Another study showed that the aqueous extract of this plant and its butanol fraction reduced the total acidity of gastric secretion, the index of mucosal damage, and the number of ulcers in pylorus-ligated mice (**Table 5S**, Supporting Information) [20]. The results also showed that the butanol fraction and its main constituents isoorientin, orientin, isovitexin, catechin, epicatechin, and procyanidin B2, B3, B5, and C1 had equal potency inhibiting gastric H+, K+ ATPase enzyme activity, when tested both individually and in a complex mixture (**Table 5S**, Supporting Information) [20]. Feltrin et al. showed that a standardized extract of this plant was able to inhibit 2 cytochrome P450 enzymes, namely CYP3A4 and CYPD6 (**Table 5S**, Supporting Information), a characteristic that may modify the bioavailability and efficacy of certain drugs [62].

There are few studies available describing the acute and chronic toxicity of the genus *Cecropia*, as well as their effect on fetal development and genotoxicity. In this regard, a hydroalcoholic extract of *C. glaziovii* and an aqueous extract of *C. obtusifolia* showed no relevant toxicity on rats nor in their litters (**Table 5S**, Supporting Information) [111–113]. Moreover, *C. obtusifolia* leaf extract was not cytotoxic nor genotoxic in either the *Drosophila* wing somatic mutation or the human micronucleus assay [114]. Additional studies showed that oral administration of an aqueous extract of the leaves of *C. pachystachya* (2 g/kg) was not genotoxic nor mutagenic in rats [115], with no sign of toxicity in mice [116]. However, doses between 0.5 to 2 g/kg caused DNA damage on brain tissue [115].

Future Perspectives

Aside from the widely recognized properties of *Cecropia* as antihypertensive and antidiabetic agents, other exciting effects highlight the industrial and pharmacological potential of the plants in this genus, making it worth encouraging their further development.

For instance, *C. pachystachya* and *C. obtusa* have been shown as promising candidates for dermo-cosmetic formulations to prevent skin aging or for photochemoprotection [66, 67]. Special interest may be given to flavonoid-rich *C. pachystachya* extracts to treat and manage skin damage, due to their capacity to produce angiogenesis, epithelialization, and collagen deposition [69].

Other promising applications include the further study of *C*-glycosyl flavonoid enriched fraction of *C. glaziovii*-loaded nanospheres and standardized hydroethanolic *C. glaziovii*-loaded PLGA microparticles as drug delivery systems to treat labial herpes and hypertension [117–119]. In these investigations, the developed particle preparations were proposed to be capable of overcoming the bioavailability, permeability, and solubility issues associated with flavonoids [118, 119]. Additionally, a magnetic emulsion nanoparticle of maghemite dispersed in an aqueous extract of *C. obtusifolia* leaves provided long-term biocompatibility and chemical stability to the extract [120]. Further research in the field of nanocomposite particles as drug delivery systems would be a fruitful and interesting area to explore.

There is also evidence that *C. pachystachya* may be useful in the prevention of bipolar disorder by reducing the episode relapse and the oxidative damage observed in its manic phase [57]; that triterpenes obtained from *C. lyratiloba* have the potential to develop multidrug resistance anticancer agents [104, 106]; and that the triterpenes from *C. telenitida* may become novel immunomodulatory/anti-inflammatory drugs [7].

Finally, the capacity of *C*-glycosyl flavonoids, rutin, and chlorogenic acid (from *C. pachystachya*) to act as quorum sensing inhibitors of *C. violaceum* and *E. coli* [108] proposes a novel biotechnological application yet to be exploited.

Conclusions

Synonymized entities or identified morphotypes in the genus *Cecropia* may represent new species. Those unresolved species complexes may lead to inaccurate taxon selection and imprecise assessments of biodiversity, conservation, biogeography, and speciation processes [121, 122]. Additionally, a bad taxonomic circumscription or an inaccurate identification could also lead to misinterpretations of the results in pharmaceutical research of natural products [123–126]. Therefore, additional taxonomic, molecular, morphological, chemical studies, extensive additional fieldwork, nomenclatural studies, and a thorough examination of specimens must be carried out to confirm their identities.

There is evidence that for the genus *Cecropia* specific secondary metabolites differ both quantitatively and qualitatively among closely related species, within a single species, and among members of a population. The phytochemical content of *Cecropia* leaves might be highly influenced by various factors such as genotypic differences, genetic aspects, climatic conditions, and harvesting methods. These factors should be further investigated to address this issue.

The therapeutic properties of the plants in this genus have generally been attributed to its chemical composition consisting mainly of terpenoids, steroids [5], chlorogenic- and caffeic acid [96], proanthocyanidins, flavonoids [3], and other phenolic compounds [15]. For instance, chlorogenic acid and isoorientin have been well identified as key constituents responsible for the hypoglycemic effect of *C. obtusifolia* and *C. peltata*. Similarly, the presence of flavonoids, catechins, proanthocyanidins, terpenic, and steroidal compounds have been associated with the antihypertensive and anti-inflammatory activities of *C. glaziovii* and *C. pachystachya*.

In several studies, synergism has been proposed as the mechanism of action for *Cecropia* extracts [58, 90]. Thus, a mixture of phytoconstituents may be responsible for the complex pharmacological effects of these extracts, and it may be the reason why it has been difficult to correlate individual compounds with specific biological activities.

Caution must be taken when comparing results from extracts obtained from different *Cecropia* species, since chemical composition may vary among species and geographical location.

Variation in the chemical composition of extracts may depend on the method of extraction but also on the species and the collection site. Although some species of this genus have enough scientific support and preliminary analytical methods to be recommended as phytomedicines, other species still require additional studies to improve the methodology to assure its quality, safety, and efficacy.

While the medicinal use of plants of this genus has been officially documented in National Pharmacopoeias and Formularies of several Latin American countries, it is important to understand that these are complex mixtures requiring a thorough understanding of their chemical composition and their correlation with their biological activities to be recognized as phytomedicines.

Supporting Information

Table 1S provides the key morphological characteristics of the genus *Cecropia*. Additionally, **Tables 2S, 3S**, and **4S** show detailed content of chemicals present in the 10 species of *Cecropia,* selected for this review. Finally, **Table 5S** summarizes the most relevant pharmacological activities of this genus.

Contributors' Statement

Conception of the work: C. Caballero-George; design: A. Rivera-Mondragon, O.O. Ortiz, M.P. Gupta, C. Caballero-George; data acquisition: A. Rivera-Mondragon, O.O. Ortiz, M.P. Gupta, C. Caballero-George; data interpretation: A. Rivera-Mondragon, O.O. Ortiz, M.P. Gupta, C. Caballero-George; drafting the manuscript: A. Rivera-Mondragon, O.O. Ortiz, M.P. Gupta, C. Caballero-George; critical revision of the manuscript: C. Caballero-George.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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