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Review Article

A REVIEW OF THE ANTI-INFLAMMATORY AND ANTIMICROBIAL ACTIVITIES OF THE COMPONENTS OF THE *CECROPIA* GENUS

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ABSTRACT

The genus *Cecropia* belongs to the Urticaceae family and has a wide diversity of species in several regions of South America. In folk medicine, they have many uses, such as hypoglycemic, antihypertensive, anti-inflammatory, and sedative. Species of the genus *Cecropia*, such as *Cecropia pachystachya*, *Cecropia glaziovii*, and *Cecropia obtusifolia*, have been the subject of several phytochemical studies, and the main isolated compounds were orientin, isoorientin, isovitexin, vitexin, as well as *c*-glycosylflavonoid compounds. These active compounds were characterized as responsible for the use of *Cecropia* plants in the treatment of inflammation and also as antimicrobial agents. This review aims to describe the main characteristics of the genus *Cecropia*, exploring the compounds responsible for the medicinal uses of these species and focusing on anti-inflammatory and antimicrobial uses.

Keywords: Urticaceae, Folk medicine, Vitexin, Orientin, Natural extracts.

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INTRODUCTION

The genus *Cecropia* belongs to the Urticaceae family and comprises approximately 100 species, being a native plant of Central and South America [1]. In general, species of the genus *Cecropia* are secondary vegetation trees, 5–25 m in size, with a segmented trunk, erect, hollow, and broad leaves, with distinct color and texture [2].

The wide diversity of species in various regions of South America combined with the ease of seed dispersal leads to stocks of several different species in the same region. [3]. Popular names vary according to the colors of the flowers and can be called red embaúba (*Cecropia glaziovii*), white embaúba (*C. palmata*), and silver embaúba (*Cecropia pachystachya*). However, there is some disagreement as to the finding of new species, as attempts to characterize a new species, *Cecropia catarinensis* did not find unanimity among different researchers [4]. Examples of specimens of different *Cecropia* species are summarized in Fig. 1.

C. pachystachya Trécul popularly known in Brazil as "embaúva," "embaúba," sloth tree, or tore, in Argentina and Bolivia as "ambaybo," and in Paraguai as "amba'y," is a tree and fruit tree with ornamental and medicinal purpose, used in folk medicine. It proliferates, mainly in Brazil and Argentina, especially in the Atlantic Forest zone [5,6]. *C. glaziovii* is an evergreen tree with a thin and open crown. The tree is harvested in the wild for local use as a source of food and various commodities. A characteristic of the genus is that because they have hollow branches, they can harbor ants. Trees attract ants by producing a honey-like sap, and ants respond by working to keep the tree free from leaf-eating pests – which may include humans [7].

Cecropia hololeuca is another representative species of the genus, who prefer a sunny position on well-drained soil. It is a fast-growing but short-lived tree. Newly planted young trees can be 3 m or more in height after 2 years. A dioecious species, both male and female forms, need to be cultivated if fruits and seeds are needed. The fruits of many members of this genus are edible and sweet. Finger-shaped aggregate fruit may be 150 mm or longer and 18 mm wide [8].

The plants of genus *Cecropia* has diverse uses in popular medicine in Latin America and continue today, which scientific research confirming various of these uses. Furthermore, some of the species of *Cecropia* are in Pharmacopeias, such as the Brazilian Pharmacopeia and Argentinean Pharmacopeia, as pharmaceutical raw material. Thus, the objective of this review is to compile and analyze scientific information about *Cecropia* species, including their chemical composition and pharmacological proprieties, focusing on the main compounds present on genus and anti-inflammatory and antimicrobial effects.

USES OF *CECROPIA* SPP

The use of plants from genus *Cecropia* in folk medicine is widespread, and several species have documented their uses for various functions. Table 1 summarizes the main species of the genus such as the main effects and chemical components. The species *C. pachystachya* is used as a diuretic, tonic, and also to treat respiratory diseases [3]. The healing property of the species was demonstrated by an ethyl acetate extract incorporated into a gel, which obtained a better re-epithelization than controls [9]. Popular uses also include its use as anti-hemorrhagic and astringent, with reports of use on episodes of tachycardia, high blood pressure, tuberculosis, wounds, fever, and other purposes [10-12]. Pharmacological effects such as anti-inflammatory, cardiotonic, and sedative effects have also been reported [13-15]. The hypoglycemic effect was shown by a methanolic extract from *C. pachystachya* in rats, in which extract demonstrated effects similar to the reference drug metformin [16].

A reduction in the activity of the angiotensin-converting enzyme (ACE) was observed in an *in vitro* model by ethyl acetate extract from the leaves of *C. pachystachya* [17]. This result was confirmed *in vivo* by Maquiaveli *et al*., which improved the renal function of rats submitted to a model of chronic renal failure, showing a decrease in ACE activity in the renal cortex [18].

C. glaziovii Snethl, another plant of the genus that is also used in popular culture, has reported use in the treatment of cough, asthma, blood pressure, as well as being used as a diuretic, cardiotonic, and anti-inflammatory [19]. Petronilho *et al*., using a hydroethanolic extract from leaves of *C. glaziovii*, showed a hepatoprotective action of this extract, which was due to high levels of antioxidant activity [20]. Two studies demonstrated the antiviral capacity of extracts from *C. glaziovii* leaves, which both in the chemical analysis indicated the presence of

Fig. 1: Exemplars of different *Cecropia* species. (a) *Cecropia pachystachya*, (b) *Cecropia glaziovii*, (c) *Cecropia obtsufolia*, and (d) *Cecropia hololeuca*

Table 1: Main constituents and activities of different *Cecropia* species

Species	Main constituents	Main activities
C. pachystachya	Orientin, isoorientin, isovitexin, vitexin, chlorogenic acid, catechin, epicatechin, procyanidins, protocatechuic acid, pomolic and oleanolic acids, and α-amyrin	Diuretic, tonic, anti-hemorrhagic, anti-inflammatory, hypotensive, sedative, cicatrizant, antimicrobial, and hypoglycemic
C. glaziovii	Orientin, isoorientin, isovitexin, catechin, epicatechin, procyanidins, and chlorogenic acid	Hypoglycemic, hypotensive, diuretic, anti-inflammatory, and antimicrobial
C. obtsufolia	Isoorientin, palmitic, stearic, vanillic acids, sitotesnone, vinyl guaiacol, o-Tolylaldehyde, and chlorogenic acid	Hypoglycemic, analgesic, central depressant, and anti-inflammatory
C. peltata	Pomolic acid, α-amyrin, β-amyrin, derivatives of stigmasterol, and chlorogenic acid	Wound healing, antiparasitic, hypoglycemic, and anti-inflammatory
C. hololeuca	Orientin and isoorientin, catechin, epicatechin, procyanidins, protocatechuic acid, and chlorogenic acid	Anti-inflammatory, diuretic, and antidiarrheal

C. pachystachya: Cecropia pachystachya, C. glaziovii: Cecropia glaziovii, C. hololeuca: Cecropia hololeuca

isorientin and isovitexin, and the antiviral effect on herpes simplex virus was linked to the presence of these chemical components [20,21].

The antihypertensive effect of *C. glaziovii* has demonstrated in rats with an aqueous extract, and the mechanism of action on animals was not due to ACE inhibition or nitric oxide (NO) synthesis but generated long-term hypotension in an l-NAME model of hypertension [22,23]. This antihypertensive effect could be explained by a vasorelaxant action promoted by a hydroethanolic extract obtained from the leaves of *C. glaziovii*, which was endothelium-dependent, confirming the need for endothelial factors to observe the phenomenon [24]. Extract from *C. glaziovii* has a bronchodilator effect, as demonstrated by Delarcina *et al.*, which inhibits bronchospasm histamine-induced in guinea pigs after treatment with aqueous extract or semi-purified fractions [25].

Cecropia obtusifolia, popularly used in rheumatic and kidney inflammation pathologies, presented an analgesic effect in chemical-induced pain, which characterizes a peripheral analgesic effect [26]. The hypoglycemic effect of this species was explored to confirm the folk use and obtained sustained results in type 2 diabetes patients after 18 weeks of use of an aqueous extract from its leaves [27]. This effect has already been demonstrated in animals [28], which showed a significant decrease in plasma glucose levels only 2–4 h after the administration of a methanolic extract.

The effects of *C. obtusifolia* on the cardiocirculatory system were observed in different studies. A methanolic extract obtained from its leaves demonstrated a hypotensive activity on rats, acting quickly as 45 min to decrease the pressure [29]. This characteristic was utilized in hypertensive rats, which have a reduction in blood pressure after few minutes of the injection of an aqueous extract, without alterations in cardiac frequency [30].

C. peltata is also present in widespread use, and one of these uses was confirmed by a study that demonstrated a decrease in blood glucose in

normal rats, showing dramatic results as a decrease of 50% of in plasma levels of glucose after 2 h [28]. Furthermore, diverse uses of *C. peltata* were found in popular medicine in Cuba, as a laxative, for example, associated with *Arundo donax* (Giant reed) or to asthma, associated with *Ficus carica* and bee's honey [31].

The use of genus *Cecropia* is mainly associated with anti-inflammatory and anti-microbial effects, which are described in detail in a section above.

ACTIVES COMPOUNDS IDENTIFIED IN THE GENUS

Species of the genus *Cecropia* have been the subject of several phytochemical studies, focusing on leaf preparations. The flavonoids isoorientin, vitexin, orientin, rutin, and scoparin were identified by an ultra-sensitive method from methanolic extracts of *C. pachystachya* and *C. hololeuca*, which also identified 32 other compounds including organic acids, flavans, glycosides *C*, and *O* glycosides [3]. High-performance liquid chromatography with diode-array detection has discovered chlorogenic acid, isoorientin, orientin, catechin, epicatechin, procyanidin, isoquercetin, isovitexin, and β-sitosterol on ethyl acetate extract from leaves of *C. pachystachya* [9]. Furthermore, the flavonoids vitexin, orientin, and isoorientin were identified in *C. schreberi*, besides triterpenoid α-amyrin and pomolic acid [32]. The main compounds isolated from *C. pachystachya* are orientin, isoorientin, isovitexin, vitexin, as well as chlorogenic acid [5,33].

These constituents may explain the biological activities found in *Cecropia* species since they have been detected in *C. pachystachya*, which demonstrated anti-inflammatory, leishmanicidal, and hypoglycemic activities [34]. Besides, these secondary metabolites are common in herbal medicines that have antioxidant and anti-inflammatory action, acting on the central nervous system, thus being considered alternative drugs for the treatment of degenerative diseases [33].

Isovitexin has already been related to an antinociceptive activity in an animal model using extracts containing high concentrations of the compound, which were able to significantly inhibit the effect of acetic acid as a pain inducer, similar to indomethacin. Some of these extracts also had isoorientin and vitexin, indicating a possible synergistic action between them [35]. The antinociceptive effect is due to interaction with opioidergic δ, κ, and μ receptors subtypes and nitrergic pathway. A study showed that an intraperitoneal irritation with acetic acid triggers the release of several mediators such as neurotransmitters and neuromodulators. These mediators increase vascular permeability, reduce the threshold of the nociception, and stimulate the nociceptive neurons sensitive to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Hence, vitexin (and probably isovitexin) significantly decreased the number of abdominal constrictions and reducing the number of writhes, which suggests that the mechanism of this flavonoid may be related with a decrease in the release of inflammatory mediators in peripheral tissues or by direct blockage of its receptors, resulting in an anti-nociceptive effect [36].

Vitexin and isovitexin exhibited anti-inflammatory effects through the inhibition of p38, extracellular signal-regulated kinases and c-Jun N-terminal Kinase (p-JNK) [37], which cause the decrease of NO, prostaglandin E2 (PGE2), interleukin (IL)-1 beta (1β), IL-6, and tumor necrosis factor-α (TNF-α) secretion [37,38]. These compounds can affect the expression of some mediators, decreasing the production of cyclooxygenase-2 (COX-2), nuclear factor kappa-B (NF-κB), inducible NO synthase (iNOS) [39,40], and increasing IL-10 secretion [38]. In a lipopolysaccharide (LPS)-stimulated mouse macrophage model, isovitexin inhibited TNF-α secretion, PGE2 formation, and iNOS activity through inhibiting the expression of NF-κB and COX-2 [39,40]. Hence, isovitexin could be explored as a new type of NSAIDs.

The flavone isoorientin demonstrated antitumor activity in an *in vitro* model of pancreatic cancer cells, inducing apoptosis of transformed cells. The mechanism of action was established and demonstrated upregulation of Adenosin Monophosphate-activated protein kinase, an intracellular sensor that, once activated, stimulates the apoptosis of the neoplastic cells [41]. Many drugs, with a specific anti-cancer activity or no, stimulate this pathway, causing apoptosis in tumors [42,43]. Yuan *et al.*, working with HepG2 cells, demonstrated that the antineoplastic effect of isoorientin is due to apoptosis induced by activation of mitogen-activating protein kinases (MAPK), specifically inactivating ERK and stimulating JNK and p38, which ultimately activate caspase-3 to kill the cells. Furthermore, reactive oxygen species stimulated by isoorientin acts as an upstream signaling molecule to initiate the MAPK signaling pathway in HepG2 cells [44].

Isoorientin has also identified anti-inflammatory activity in a TNF-α-induced keratinocytes model, decreasing the secretion of IL-6, vascular endothelial growth factor, and IL-8, that *in vivo*, are responsible for angiogenesis in epidermal cells activate by TNF [45]. The anti-inflammatory effect of isoorientin was confirmed in a carrageenan *in vivo* model, in which edema caused by the chemical was partially inhibited by the compound, with a similar effect of the indomethacin, a knowledge NSAID. Furthermore, the isoorientin did not show gastric damage, a common collateral effect of NSAID [46]. Recent studies have confirmed the anti-inflammatory activity of orientin, which was able to diminish inflammatory markers (NF-κB, TNF-α, IL-6, iNOS, and COX-2) in the homogenate of colorectal cancer cells of rats [47] or macrophages RAW264.7 [48] treated with orientin.

Another characteristic showed by isoorientin, and orientin was the inhibition of quorum sensing (QS) formation. A study demonstrated that both compounds could inhibit, *in vitro*, the formation of QS by *E. coli*, although they did not present antimicrobial activity. This characteristic is important, once QS is involved in chronic infection and the formation of biofilm [49].

Thus, the triterpenoid amyrin showed anti-inflammatory and antinociceptive actions in an animal model when used orally, inhibiting the migration of the leukocytes and decreasing the pain of the animals induced by carrageenan and acetic acid, respectively [50]. It was also found that extracts with a high concentration of amyrin present leishmanicidal activity, acting both in the promastigote (extracellular) and amastigote (intracellular) forms [51].

THE ANTI-INFLAMMATORY ACTIVITY

The use of plants from the genus *Cecropia* to treat inflammation has been proposed for a long time in popular culture [52], and some studies have already presented scientific evidence supporting this use. There are many species of *Cecropia* involved in the anti-inflammatory process, such as *C. pachystachya* [5,9,18,53-55], C*. obtusifolia* [26], *C. peltata* [56], *C. glaziovii* [1], and *C. hololeuca* [57]. Table 2 summarizes the main studies showing the anti-inflammatory activity of species from the genus *Cecropia*.

Several models to induce inflammation were proposed, and the extracts of *C. pachystachya* have been showing to interfere with the inflammatory process of these models, showing anti-inflammatory effects *in vivo* and *in vitro*. Pacheco *et al.* showed one evidence that the methanolic extract of *C. pachystachya*, in a concentration of 0.1 mg/ear, in Swiss mice, promoted a decrease in the acute inflammation in ear edema induced by croton oil or arachidonic acid, with a decrease similar to the medicines usually used as controls, dexamethasone, and indomethacin, respectively. These animals also showed a decrease in the inflammatory infiltrates, as seen by histochemical analysis of the injured ear. Moreover, such extracts promoted *in vitro* antioxidant activity seen by the 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) technique [5].

The application of croton oil to induce edema and local inflammation has been widely used. It promotes local inflammation and edema, with polymorphonuclear infiltration, inflammatory mediators releases, such as leukotrienes, PGE2, histamine, and others [58]. As long with that, another

Table 2: Anti-inflammatory effects of different *Cecropia* specie

Species/extract	Model	Inflammation inductor	The components in the plant	Effect	Reference
C. pachystachya leaves, methanolic extracts	Ear edema *in vivo*	Croton oil *in vivo*	Polyphenols (chlorogenic acid). Flavones (C-glycosylated, orientin, and isoorientin)	Anti-inflammatory and antinociceptive	[16] Aragão *et al.,* 2010; [54] Aragão *et al.,* 2013
C. pachystachya leaves, ethyl acetate extract	Excision skin wounds *in vivo* model	Mechanical exposition of fascia supercialis in the dorsal region, exposing epidermis, dermis, hypodermis, and muscular layer	Polyphenols (chlorogenic acid). Flavones (orientin and iso-orientin)	Anti-inflammatory. Antioxidant. Anticipation in the healing process	[9] Duque *et al.,* 2016
*C. pachystachy*a leaves, aqueous extracts	Progressive kidney injury *in vivo*	Kidney injury: an infarction was provoked in two-thirds of the left kidney by ligation of one or two branches of the left renal artery *in vivo*	Polyphenols (Phenolic acid-chlorogenic acid). Flavones (orientin)	Anti-inflammatory, decrease in the expression of pJNK	[18] Maquiaveli *et al.,* 2014a
C. pachystachya leaves, methanolic extracts	Ear edema *in vivo*.DPPH *in vitro*	Croton oil and arachidonic acid *in vivo*	Polyphenols (Phenolic acid-chlorogenic acid). Flavones (orientin and isoorientin)	Anti-inflammatory. Antioxidant	[5] Pacheco *et al.,* 2014
C. obtusifolia leaves, aqueous extracts	Hyperglycemia *in vivo*	Hyperglycemia induced by Streptozotocin *in vivo*	Polyphenols (chlorogenic acid)	Reduction in TNF-alpha, increase in IL-10, and adiponectin	[65] de Los Ángeles Fortis-Barrera *et al.,* 2019
C. obtusifolia leaves, aqueous extracts	Rat paw edema	Paw edema induced by carrageenan *in vivo*	Not described	Anti-inflammatory, reduction in edema	[26] Pérez-Guerrero *et al.,* 2001
C. peltata leaves, aqueous, and methanolic extracts	Wound	Excision wound criteria. The full thickness of 2.5 cm length and 0.2 cm depth of the excision wound was created along the markings using toothed forceps, a surgical blade, and pointed scissors *in vivo*	Not described	Anti-inflammatory. Anticipation in the healing process	[56] Nayak, 2006
C. glaziovii leaves, aqueous extracts	Pleurisy *in vivo* DPPH *in vitro*	Carrageenan-induced pleurisy *in vivo*	Polyphenols (chlorogenic acid). Flavones (isovitexin and iso-orientin)	Anti-inflammatory, decrease in leukocyte infiltration and pro-inflammatory cytokines such as TNF-alpha and IL-1beta	[1] Müller *et al.,* 2016
C. hololeuca aqueous extracts	Paw edema *in vivo* LPS in macrophages J774.A *in vitro*	Carrageenan-induced paw edema *in vivo*	Phenolic compounds (gallic acid, caffeic acid, catechin)	Anti-inflammatory Reduction *in vitro* of TNF-alpha, IL-1 beta, and nitrite release. Reduction in edema	[57] Machado *et al.,* 2019

C. pachystachya: Cecropia pachystachya, C. glaziovii: Cecropia glaziovii, C. obtusifolia: Cecropia obtusifolia, C. hololeuca: Cecropia hololeuca, LPS: Lipopolysaccharide, DPPH: 2,2-diphenyl-1-picryl-hydrazyl-hydrate

study showed that the extracts from *C. pachystachya* probably affect the mechanisms of inflammatory mediators by reducing inflammatory cells [5]. Another fact that reinforces this hypothesis is that the extracts of *C. pachystachya* used in this study showed high levels of polyphenols that are known to be antioxidants and act as reducing agents through several mechanisms, including eliminating free radicals together with the capacity to inhibit many enzymes involved in the pro-inflammatory cascade [59].

In another study, Wistar rats submitted to progressive kidney injury had a less exacerbated inflammatory process when treated with *C. pachystachya* water extracts, composed of polyphenols (chlorogenic acid) and flavones (orientin), compared to the untreated rats [18]. Such attenuation of the inflammatory process by *C. pachystachya* extracts was related to a decrease in the expression of p-JNK and the increase in renal arginase activity [53].

Furthermore, showing the presence of flavones (C-glycosylated, orientin, and isoorientin) and polyphenols (chlorogenic acid), other studies pointed out that the use of *C. pachystachya* extracts resembles the effects of a reference anti-inflammatory in a croton oil-induced ear edema model. The extract used was applied topically (1 mg/20 μL) and orally (300 mg/kg) in Swiss mice, probably under the mechanisms of lipoxygenase and cyclo-oxygenase inhibition [16,60]. Aragão *et al.*, still showed an antinociceptive effect of the extracts from *C. pachystachya* under the animal model of acetic acid-induced writhing and formalin-induced pain, they showed a decrease in the nociceptive by the animals [54].

The dichloromethane extracts of *C. pachystachya*, used orally, also showed efficacy as an anti-inflammatory in an animal model of carrageenan-induced paw edema [55]. Likewise, the extract of *C. pachystachya* through an oral application, promoted a decrease in IL-1β release in the local of inflammation and also decrease nitrite secretion in an *in vitro* assay using macrophages RAW 264.7, but did not alter PG release. The component isolated in this extract was from the class of triterpenes, the pomolic acid [55]. The carrageenan

inflammation model is mediated mainly by free radicals release, PG, and nitrite, leading to edema and inflammatory cell infiltration [61,62].

The use of a *C. pachystachya*-based gel to improve the healing process in Wistar rats with an open wound triggered by mechanical injury has also been evidenced. The treatment accelerated the process of tissue repair, promoting a lower degree of cellularity that improves the local inflammatory tissue. The main components of this ethyl acetate extract of *C. pachystachya* were flavones and polyphenols. Normally, the main mechanism of local inflammation lies in the increase of capillary permeability and cell migration to the local inflammation. The extracts of *C. pachystachya* improved homeostasis, interfering in the construction of new tissue, leading to a short inflammatory stage, promoting anticipation in immune cell recruitment and the process of repair. Another mechanism of these extracts lies down on the deposition of collagen and fibroblast proliferation, with early and significant angiogenesis, seen by the histopathological analysis [9].

The use of extracts from leaves of another species of *Cecropia*, *C. obtusifolia*, showed its anti-inflammatory action used either topically in a croton oil-induced ear edema model or as a systemic therapy through oral in a mouse paw edema carrageenan-induced model. Still, the anti-inflammatory effect can be explained by a capacity of the extract to interfere with the synthesis and secretion of inflammatory mediators, such as histamine and PGs [26].

When it comes to the healing process, Nayak showed that aqueous and ethanolic extracts of *C. peltata* used topically and aqueous extracts used orally, both at a dosage of 150 mg/kg, for the treatment of skin lesion in rats, promoted rapid wound reduction, with a better healing process and low amount of tissue granulation and dead tissue, compared to carboxymethylcellulose, used as control [56]. The acceleration in the healing process by the extracts of *C. peltata* can be explained by an increase in protein, hydroxyproline, and hexosamine in the lesions, with anticipation in collagen deposition.

Still, other *Cecropia* species also presents anti-inflammatory effects. In an animal model of pleuritis, the treatment with aqueous extracts of *C. glaziovii* reversed the inflammation caused by carrageenan *in vivo* as well as showed antioxidant effects *in vitro*. Containing polyphenols (chlorogenic acid) and flavones (isovitexin and isoorientin), the mechanism behind *C. glaziovii* action is the anti-inflammatory effect by inhibition of the migration of leukocytes together with the decrease in inflammatory mediators such as nitrite and cytokines as TNF-α and IL-1β to the inflammation site [1].

In vitro tests on J77A.1 macrophages showed that aqueous extract of *C. hololeuca* promoted inhibition of LPS-stimulated NO secretion by up to 40%, as well as decreased secretion of pro-inflammatory cytokines such as TNF-α and IL-1β [57]. The presence of phenolic compounds such as gallic acid, caffeic acid, and catechin, contributes to the anti-inflammatory action of this extract. Machado *et al*. also showed an *in vivo* analysis of the anti-inflammatory capacity of *C. hololeuca* extracts on carrageenan-induced paw edema in mice Balb/c, demonstrating the benefits in reducing the edema on these animals. The mechanism that explains this action is related to the capacity of the extracts in reducing pro-inflammatory mediators [57] mainly because of the presence of gallic and caffeic acid, as it was previously shown to be responsible for reducing edema inflammation [63,64].

In another set of way, de Los Ángeles Fortis-Barrera *et al.* performed experiments to verify the hypoglycemic effect of aqueous extracts from the leaves of *C. obtusifolia*, concluding that extracts were effective mainly because of its anti-inflammatory capacity, modulating the mediators of inflammation, increasing IL-10 and adiponectin, and decreasing TNF-α in the serum. Here, the hyperglycemic mice received the treatment by injection of the extract (200 mg/kg) through intraperitoneal and were compared to a control group, and another group treated with the reference drug for hyperglycemia (metformin) [65].

THE ANTIMICROBIAL ACTIVITY OF *CECROPIA* SPP

Supporting the anti-inflammatory effect, extracts of different species of the *Cecropia* genus can also present antimicrobial activity [52,66]. The extracts of *C. paltata* presenting steroids and amino acids and inhibited the growth of *E. coli* in the aqueous, ethanolic, and hexane extracts. Furthermore, the ethanolic extracts had antimicrobial effects on *Staphylococcus aureus* and *Bacillus cereus*, while the hexane extract of *C. peltata* had the antimicrobial effect on *Streptococcus* β-hemolytic and *Candida albicans*. Still, the minimum inhibitory concentration (MIC) of *C. peltata* ethanolic and hexane extracts on *E. coli* strains was statistically the same comparing to the reference drugs [66]. Indeed, the species *C. peltata* showed an intermediate zone of inhibition over *Neisseria gonorrhoeae*, the pathogen responsible for the development of gonorrhea [67].

A study showed that *C. pachystachya* methanolic fractions alone did not show antimicrobial activity but, associated with aminoglycosides, showed a synergic activity against *S. aureus* by reducing the MIC of the antibiotic through the microdilution method [6]. Another study showed that *C. pachystachya* extracts, especially methanolic, presented the components chlorogenic acid (which is a cinnamic acid), isoorientin, orientin, isovitexin and vitexin (glycosylated flavonoids), and rutin (C-diglycosylated flavonoids). In the growth inhibition assay, these extracts did not have a potent inhibition property against *Pseudomonas aeruginosa* ATCC 27853 and *S. aureus* ATCC 25923 and no inhibitory activity against the yeast *Saccharomyces cerevisiae* as well [49].

The butanolic extracts of *C. glaziovii* showed the presence of isoorientin and isovitexin, both *c*-glycosylflavonoids compounds, phenolic acids, and procyanidins, while the methanolic fractions showed only c-glycosylflavonoids, isoorientin, and isovitexin. Both extracts of *C. glaziovii* leaves showed antiherpes activity, but the methanolic extract was the most potent agent against herpes virus types 1 and 2. The reason behind this is related to the high concentration of c-glycosylflavonoids, showing a selectivity index of 131 against Herpes Simplex Virus type 1 and 67 to type 2. However, it was only against the HSV-2 that the methanolic extract of *C. glaziovii* had an inhibitory effect directly to the virus, with an IC_{50} of 18.75 μg/mL. Furthermore, this *C. glaziovii* methanolic extract had a potent effect on the infectivity capacity of HSV types 1 and 2, decreasing the attachment and binding of the virus on the cell and also, it prevented the penetration of the virus to the cell, it also prevented viruses from spreading cell to cell [68].

Another research showed the antimicrobial action of hydroethanolic extract of *C. glaziovii* on the replication of herpes simplex virus type 1 replication in the cell line Vero, with a selectivity index of 50. The main compound present in these extracts was isoorientin, orientin, isovitexin, and chlorogenic acid [20]. The main responsible for the antiviral activity is the phenolic compounds, as it has been proposed before [69,70], and this compound in the extracts of *C. glaziovii* the main responsible for the antiviral effect [20]. Exploring the antiviral capacity of *C. glaziovii*, dos Santos *et al.* showed that the *c*-glycosylflavonoid enriched fraction of *C. glaziovii* inhibited the replication of HSV-1 by 100% at a concentration of 80 μg/mL, with an inhibitory concentration (IC_{50}) of 8.24 μg/mL [21].

Cecropia genus was also potent against some parasites too [34,69-71]. Indeed, *Cecropia obtusa* was one of the main cited plants used to treat *Leishmania* infection on an ethno research that aimed to know the main plants used to treat leishmaniasis in the Oyapock basin (French Guiana) [52].

Ethyl acetate fraction extracts of *C. pachystachya* presenting the compounds apigenin, orientin, and isovitexin, showed *in vitro* leishmanicidal effects with an IC_{50} of 53 μg/mL on promastigote forms, which was lower than the pentostan (IC_{50} > 64 μg Sb^{v}/mL), but higher than amphotericin (IC_{50} 0.65 μg/mL). This effect appears to be directly linked to the arginase inhibition and interference with the parasite mitochondrial DNA [71].

Although, Ribeiro *et al.* did experiments with the extracts of *C. pachystachya* and showed no antileishmanial activity, when the promastigotes were cultivated under different concentrations of the extract for 48 h [72]. Cruz *et al.* did an incubation of 72 h, used an amount of 10^5 cells per well and the parasites were in a logarithmic-phase culture, whereas Ribeiro *et al.* incubated the promastigotes for 48 h, with a density of 5×10^5 cells per well, and used stationary promastigotes, this difference in the protocols can explain the different outcome of both studies [71,72].

It was also showed that the ethanolic extracts of *C. peltata* and *C. metensis* had an antimalarial activity. Against *Plasmodium falciparum*, the ethyl acetate fractions were the extract with this potential activity, with an IC_{50} of 12.12 µg/mL from *C. membranacea* and 12.52 µg/mL from *C. metensis*, while the chloroquine, the drug used to treat malaria, had an IC_{50} of 1.48 µg/mL. These extracts showed a mixture of flavonoids, tannins, and triterpene compounds. It has been shown that the flavonoids compounds are one of the most evident contributors to the activity, but the presence of terpenes and tannins probably potentiates this activity [73].

Agreeing with that, extracts of *C. pachystachya* showed antimalarial activity *in vivo*, using ethanolic extracts from its wood, roots, and leaves, as the most active was the roots. The respective extracts showed to reduce the parasitemia by 35–66% compared to the non-treated control mice. The following compounds, β-sitosterol, and tormentic acid, presented in the root extract, showed to be essential for its antimalarial activity. However, only the tormentic acid inhibited the growth of the parasite *P. falciparum* chloroquine-resistant (W2) in culture, leading to a decrease in the parasitemia, with an IC_{50} of 15 µg/mL [34].

An ethanolic extract of *C. pachystachya* showed activity against *S. aureus*, which was explained by the presence of secondary metabolite compounds such as flavonoids, which have significant antimicrobial activity. This activity could be explained by the solubility of phenolic groups, which have a protein affinity, that works inhibiting bacterial enzymes [74,75].

FUTURE PROSPECTIVES

It has been demonstrated that plants from the genus *Cecropia* possess a great variety of components with a wide range of functions, such as anti-inflammatory, antimicrobial, hypoglycemic, and hypotensive. These characteristics are extensively explored by traditional medicine, but it has not been explored enough to be applied in pharmaceutical research aiming a commercial application.

Thus, it is important to refine the studies involving species of *Cecropia* genus, focusing on clinical trials, and directing to pharmaceuticals formulas with an easy distribution and low cost.

CONCLUSION

The genus *Cecropia* has several essential species, which are used to treat diseases in folk medicine, which has led to studies to analyze its active compounds. These compounds were characterized meanly as flavones, as orientin, isoorientin, vitexin, and isovitexin. Hence, the action of these substances explains the potent anti-inflammatory and antimicrobial activities showed by the *Cecropia* genus. However, studies are needed to analyze other effects of their compounds.

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AUTHORS' CONTRIBUTION

All the authors have contributed to the literature review, preparation, and editing of the manuscript.

CONFLICTS OF INTEREST

All authors have none to declare.

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