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Angiotensin-converting enzyme inhibition by Brazilian plants

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Abstract

The potential antihypertensive activity of Brazilian plants was evaluated in vitro by its ability to inhibit the angiotensin-converting enzyme (ACE). Forty-four plants belonging to 30 families were investigated. Plants were selected based on their popular use as antihypertensive and/or diuretics. The following plants presented significant ACE inhibition rates: *Calophyllum brasiliense*, *Combretum fruticosum*, *Leea rubra*, *Phoenix roebelinii* and *Terminalia catappa*.

Keywords: Angiotensin-converting enzyme inhibition; Colorimetric assay; Brazilian flora

1. Introduction

The role of the rennin–angiotensin system (RAS) in cardiovascular physiology is well established. The angiotensin-converting enzyme (ACE), a component of RAS, catalyzes the formation of the strong pressor agent angiotensin II from angiotensin I, contributing to the maintenance of normal blood pressure [1,2].

Several ACE inhibitors such as captopril, enalapril, lisinopril and temocapril are in clinical use for the treatment of hypertension. All of these drugs produced side effects, thus justifying the search for natural ACE inhibitors for safe and economical use [1–4].

A number of compounds from plants has been identified to possess in vitro ACE inhibitory activity, including hydrolysable tannins, phenylpropanes, proanthocyanidins, flavonoids, xanthones, fatty acids, terpenoids, alkaloids oligosaccharides and peptide amino acids, among others [3,5]. Nevertheless, only a few works on bioprospecting plant species for this molecular target has been reported [5–10]. In this context, plants occurring in Brazil may represent an outstanding opportunity of finding new leads for the development of antihypertensive drugs, since the country is considered to have a rich flora.

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Table 1
Angiotensin-converting enzyme (ACE) inhibitory activity of Brazilian plants extracts

Family	Plants	Plant part	% ACE inhibition [a]	Collection data		
				Month/year	Site	Voucher number
Agavaceae	*Agave americana* L.	Leaves	–	May 02	1	BHCB 4754
Anacardiaceae	*Mangifera indica* L.	Aerial parts	8.6±8.6	Sep. 01	1	BHCB 4413
		Stems	23.9±15.7			
	Schinus terebinthifolius Raddi	Aerial parts	19.1±7.0	Sep. 01	1	BHCB 2673
Annonaceae	*Anaxagorea dolichocarpa* Sprague et Sandwith	Stems	21.8±19.7	Jan. 97	2	BHCB 1581
Araliaceae	*Didymopanax macrocarpum* Seem.	Leaves	5.7±11.4	Feb. 02	3	BHCB 3828
		Stems	45.6±6.5			
	Schefflera actinophylla (Endl.) Harms	Leaves	14.0±48.2	Nov. 99	1	BHCB 2659
		Stems	44.6±11.6			
Bignoniaceae	*Memora fulgens* Bureau	Fruits	13.0±11.7	Apr. 02	1	BHCB 2544
	Pyrostegia venusta Miers.	Stems	31.6±30.8	Feb. 02	3	BHCB 2486
	Tabebuia serratifolia (Vahl) Nicholson	Stem bark	14.3±2.2	Aug. 96	1	BHCB 1357
Caesalpiniaceae	*Cassia fistula* L.	Aerial parts	18.7±31.6	Sep. 01	1	BHCB 2676
	Senna alata (L.) Roxb.	aerial parts	–	May 02	4	BHCB 4750
		Stems	40.6±17.7			
	Senna obtusifolia (L.) H.S. Irwin et Barneby	Aerial parts	12.3±22.1	May 02	5	BHCB 4765
Caricaceae	*Carica papaya* L.	Stems	23.3±6.2	Feb. 02	3	BHCB 4625
Casuarinaceae	*Casuarina equisetifolia* L.	Aerial parts	9.6±8.9	Sep. 01	1	BHCB 2788
		Stems	28.2±6.6			
Cecropiaceae	*Cecropia glaziovii* Sneth.	Leaves	44.9±10.8	Mar. 02	1	BHCB 4063
Clusiaceae	*Calophyllum brasiliense* Cambess.	Leaves	33.5±1.5	Feb. 02	3	BHCB 3439
		Stems	54.9±16.3			
Combretaceae	*Combretum fruticosum* (Loefl.) Stuntz	Leaves	53.8±5.9	Jul. 98	1	BHCB 2292
		Stems	23.0±1.7			
	Terminalia catappa L.	Aerial parts	56.3±31.4	Sep. 01	1	BHCB 2818
Commelinaceae	*Commelina diffusa* Burm.	Aerial parts	18.3±9.9	Jul. 98	1	BHCB 2289
	Tradescantia zebrine Hort. Ex Loud.	Aerial parts	24.6±8.8	Jul. 98	1	BHCB 2294
	Tripogandra elata D.R. Hunt	Aerial parts	–	Feb. 96	1	BHCB 1144
Ebenaceae	*Diospyros hispida* A. DC.	Stems	18.0±42.4	Feb. 96	3	BHCB 4099
	Diospyros inconstans Jacq.	Leaves	8.9±7.6	Sep. 01	1	BHCB 2848
		Stems	6.8±29.2			
	Diospyros sericea A. DC.	Leaves	49.7±5.7	Feb. 02	3	BHCB 2849
		Stems	19.1±4.7			
Euphorbiaceae	*Croton antisyphiliticus* Mart.	Aerial parts	31.6±8.5	Jul. 98	1	BHCB 2293
Labiatae	*Ocimum gratissimum* L.	Aerial parts	–	May 02	1	BHCB 4755
Lauraceae	*Persea americana* Miller	Leaves	25.1±4.6	Sep. 01	1	BHCB 4412
		Stems	39.0±5.6			
Leeaceae	*Leea rubra* Bl. Ex Spreng.	Aerial parts	57.0±12.5	Sep. 01	1	BHCB 4416
Liliaceae	*Tulbaghia violaceae* Harv.	Aerial parts	35.7±15.4	Sep. 01	1	BHCB 4420
Loganiaceae	*Buddleja stachyoides* Cham. et Schltdl.	Leaves	22.7±25.7	May 02	1	BHCB 2291
Lythraceae	*Cuphea cartagenensis* Cham. et Schltdl.	Aerial parts	9.6±8.5	May 02	1	BHCB 2282
Nyctaginaceae	*Boerhavia diffusa* L.	Aerial parts	14.3±2.1	May 02	5	BHCB 4833
Palmae	*Phoenix roebelinii* O'Brien	Leaves	79.7±7.4	Sep. 01	1	BHCB 3133
Papaveraceae	*Argemone mexicana* L.	Aerial parts	–	May 02	1	BHCB 4752
Passifloraceae	*Passiflora edulis* Sims	Aerial parts	–	Dez. 01	6	BHCB 4508
Rubiaceae	*Coffea arabica* L.	Leaves	34.5±30.3	Sep. 01	1	BHCB 4415
Rutaceae	*Murraya paniculata* (L.) Jack	Aerial parts	39.0±8.4	Sep. 01	1	BHCB 4414
Sterculiaceae	*Dombeya wallichii* (Lind.) Benth. et Hook.	Aerial parts	34.7±6.2	Sep. 01	1	BHCB 2847
	Theobroma cacao L.	Leaves	24.9±21.2	Sep. 01	1	BHCB 3956
Tiliaceae	*Triumfetta semitriloba* Jacq.	Aerial parts	–	Mar. 02	7	BHCB 4627
Vitaceae	*Vitis labrusca* L.	Leaves	30.9±27.9	Dez. 01	8	BHCB 4507
Zingiberaceae	*Alpinia purpurata* K. Schum.	Aerial parts	8.7±5.3	Sep. 01	1	BHCB 2445
	Alpinia zerumbet (Pers.) B.L. Burtt et R.M. Sm	Aerial parts	2.2±1.4	Sep. 01	1	BHCB 2290
	Hedychium coronarium K.D. Koenig	Aerial parts	37.7±1.4	Jan. 02	1	BHCB 4509

[a] Final concentration of the extract solution in the ACE inhibition assay was 0.10 mg/ml. Data presented are the mean of at least three replicates ±standard deviation. (–), no inhibition detected at the assayed concentration. Collection sites: 1, UFMG *campus*; 2, São Gonçalo do Rio Doce (MG); 3, São Gonçalo do Rio Preto (MG); 4, São Gonçalo do Rio Abaixo (MG); 5, Januária (MG); 6, Charqueada (SP); 7, Caeté (MG); 8, Piracicaba (SP).

Various methods have been reported for the measurement of ACE activity. The HPLC assay developed by Elbl and Wagner [11] with further improvement [6,10] is the most employed test for plant extract screening in the search for ACE inhibitors. Limitations of the HPLC assay for evaluating a large number of samples include the analysis time and the enzyme cost, what have led us to validate a colorimetric assay for this purpose [12]. Hence, the main goal of the present work was to carry out a screening of plants occurring in Brazil with potential ACE inhibitory activity.

2. Experimental

2.1. Plants

Calophyllum brasiliense Cambess (Clusiaceae), *Combretum fruticosum* (Loefl.) Stuntz (Combretaceae), *Leea rubra* Bl. Ex Spreng. (Leeaceae), *Phoenix roebelinii* O'Brien (Arecaceae) and *Terminalia catappa* L. (Combretaceae). The plants were collected and identified by Dr. J. A. Lombardi, Departamento de Botânica, ICB, UFMG, Belo Horizonte, Brazil, in several locations of Minas Gerais (MG) and São Paulo (SP) states, as reported in Table 1. Voucher specimens of the collected plants are deposited in the BHCB Herbarium, ICB, UFMG, Belo Horizonte, Brazil.

2.2. Extraction

C. brasiliense (stems, 54.9±16.3%), *C. fruticosum* (leaves, 53.8±5.9 %), *L. rubra* (aerial parts, 57.0±12.5%), *P. roebelinii* (leaves, 79.7±7.5%), and *T. catappa* (aerial parts, 56.3±31.4%) separately were washed in water, dried at 40 °C and powdered. 10 g of each plant material were extracted with EtOH under sonication (3×15 min), The solvent was removed in vacuo to obtain the corresponding extracts kept at −20 °C. For screening, the extracts were dissolved in 20% MeOH and 80% HEPES [N-(2-hydroxyethyl)piperazine-N'-2-ethanesulfonic acid)] to a concentration of 1.1 mg/ml. The concentration, in the assay, was 0.10 mg/ml.

2.3. ACE inhibition assay

The in vitro assay used in this study is based on the cleavage of the substrate hippuryl-glycyl-glycine by ACE and subsequent reaction with 2,4,6-trinitrobenzenesulfonic acid (TNBS) to form 2,4,6-trinitrophenyl-glycyl-glycine, whose absorbance is determined at 415 nm in a microtitre plate reader [12]. Rabbit lung dehydrated by acetone (Continental Produtos Biológicos, Brazil) was employed as enzyme source.

Briefly, an aliquot of the rabbit lung solution (1 g/10 ml) was added to an eppendorf flask containing the extract solution (1.1 mg/ml) to be tested. Phosphate buffer (50 mmol/l, pH 8.3) and captopril (64 nmol/l) were employed as negative and positive controls, respectively. The enzymatic reaction was started by adding the assay buffer and the substrate solution Hip–Gly–Gly (100 mmol/l) (Sigma, USA). After homogenization, the mixture was incubated for 35 min, at 37 °C. The reaction was stopped by the addition of sodium tungstate (100 g/l) and sulfuric acid (0.33 mmol/l). After centrifugation, an aliquot of the supernatant was placed into a microtitre plate and mixed with the color reagent TNBS (Sigma, USA). After 20 min in dark, the plate absorbance was read in a microtitre plate reader (BioRad, Model 550) at 415 nm against a blank solution similarly prepared, except by adding the sodium tungstate and the sulfuric acid solutions before the rabbit lung solution. Assays were carried out at least in triplicates and a blank assay was performed for each group of 5 extracts tested.

3. Results and discussion

The potential antihypertensive activity of plant species occurring in Brazil was evaluated by the inhibition of the angiotensin converting enzyme (ACE), using a colorimetric assay [12].

Species selected for study comprised plants used in Brazil as antihypertensive and/or diuretics. Forty four plants belonging to 30 family were investigated (Table 1) and among them *A. americana*, *A. mexicana*, *B. diffusa*, *C. brasiliense*, *C. papaya*, *C. fistula*, *C. equisetifolia*, *C. glaziovii*, *C. carthagenensis*, *D. hispida*; *H. coronarium*, *M. indica*, *P. edulis*, *P. americana*, *S. alata*, *S. obtusifolia*, *T. catappa*, *T. cacao*, *T. semitriloba* and *T. violacea* were selected based on their traditional use.

Five out of the 54 investigated extracts presented ACE inhibition rates around 50%, at a concentration of 0.10 mg/ml (Table 1). Most of the ACE inhibiting plants reported in literature have been screened using the HPLC assay developed by Elbl and Wagner [11], employing plant extract concentration of 0.33 mg/ml. According to the authors, extracts with inhibition rates between 50% and 100% deserve further investigation, aiming at the isolation of the active compound(s). Despite assaying less concentrated samples (0.10 mg/ml), the criterion adopted by Elbl and Wagner [11] was followed in the present study. Hence, extracts with inhibition rates around 50% were considered active, i.e. *C. brasiliense* (stems, 54.9± 16.3%), *C. fruticosum* (leaves, 53.8±5.9%), *L. rubra* (aerial parts, 57±12.5%), *P. roebelinii* (leaves, 79.7±7.5%) and *T. catappa* (aerial parts, 56.3±31.4%). Captopril, employed as positive control in the assays, presented IC_{50}=21.2 nmol/l.

C. brasiliense is an arboreal species which grows in mountain regions and tropical forests from Southern Mexico to Brazil, popularly named guanandi, jacareúba and olandim in the country [13]. The species is traditionally used to treat several ailments as bronchitis, gastric and hepatic disturbances, pain, inflammation, diabetes, diarrhea, herpes, rheumatism and hypertension [14].

Several biological activities have already been reported for *C. brasiliense*, such as antiulcer, cytoprotective [15], antitumoral [16,17], antimicrobial [18] and antispasmodic effects [19]. As far as we know, no study supporting the popular use of the species as antihypertensive has been published to date.

On the other hand, *Calophyllum tacamahaca*, a plant popularly used as diuretic in the Réunion Islands, showed in vitro ACE inhibiting activity [7]. Hence, the ACE inhibitory activity of *C. brasiliense*, here described for the first time, seems to substantiate the popular use of the species to treat hypertension.

From the bark and heartwood [13,17] of *C. brasiliense* were isolated xanthones as **1**, **2**, whereas from the bark latex were obtained chromanone carboxylic acids [20]. Moreover, from the leaves were obtained amentoflavone (**3**), quercetin (**4**) (Fig. 1), and phenolic acids, coumarins, triterpenoids and a biflavonoid [21,22] (Fig. 1).

Several xanthones and other polyphenols isolated from *C. brasiliense* fulfill the structural requirement credited for ACE inhibiting activity and might be regarded as the active compounds from the species. Besides, the ACE inhibiting activity of amentoflavone (**3**), quercetin (**4**) and its glycosides has been previously reported [23–25], supporting the participation of these compounds on the ACE inhibitory effect.

C. fruticosum is a woody creeper, broadly distributed in tropical and subtropical regions, from Mexico to Argentina [26]. In Brazil, it receives the vulgar names of escovinha, escova-de-macaco-alaranjada and flor-de-fogo. Several species of *Combretum* are used in folk medicine to treat abdominal and lumbar pains, cough, conjunctivitis, diarrhea, dysmenorrhea, ear pain, fever, headache, ancylostomiasis, Hanse's disease, pneumonia, syphilis and general weakness [27,28]. No record was found on the traditional use of *C. fruticosum* to treat hypertension.

Although no phytochemical data has been reported for *C. fruticosum*, studies on other *Combretum* species resulted in the isolation of tannins, saponins [29], triterpenes [27] and flavonoids [30]. Compounds belonging to these classes of natural products have been described to possess ACE *in vitro* inhibiting activity and, for this reason, *C. fruticosum* was selected for screening. Among the compounds isolated, *C. erythrophyllum* furnished several flavonoids [30], which deserve evaluation of their ACE inhibition activity, namely apigenin, genkwanin, 5-hydroxy-7,4′-dimethoxyflavone, rhamnocitrin, kaempferol, quercetin-5,3′-dimethylether and rhamnazin. Similarly, alpinetin, chalcone derivative and pinocembrin, isolated from *C. albopunctatum* [31] are potentially ACE inhibiting compounds.

T. catappa is employed as ornamental species in tropical cities. In Brazil, it receives the popular names of amendoeira brava, amendoeira tropical, amendoeira da Índia, amendoeira do pará and chapéu de sol, among others [32]. The traditional use of the species to treat hypertension or associated conditions has not been described for Brazilian populations. *T. catappa* is used in the Réunion Islands as antihypertensive and diuretic, and the water extract from their leaves produced 80% of ACE inhibition, at the concentration of 0.33 mg/ml [7]. In the present work, a significant ACE inhibiting activity (56.3±31.4%) is reported for the ethanol extract from aerial parts of the species, assayed in a lower concentration (0.10 mg/ml).

On the other hand, other *Terminalia* spp., like *T. arjuna*, are used in Ayurvedic medicine to treat cardiac disorders. The alcoholic extract from its barks produced hypotension in dogs [33]. Moreover, *Terminalia bialata* bark and *Terminalia chebula* fruit, both traditionally used in India as antihypertensive, have been described to possess ACE inhibitory activity, with inhibition rates of 86% and 68%, respectively [9].

Phytochemical studies carried out with *Terminalia* spp. indicate the species as a source of polyphenols, including flavonoids as quercetin (**4**) and kampferol, along with the tannins arjunin and punicalin [34]. Based on the reported ACE inhibiting activity of polyphenols, it is feasible to suppose that structure related compounds are responsible for the activity here reported for *T. catappa*.

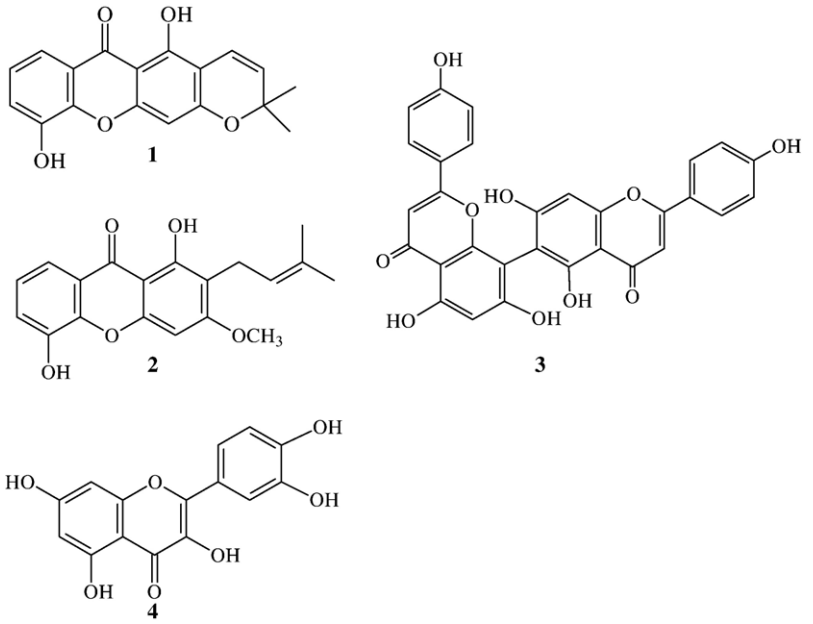

Fig. 1.

The Asian species *L. rubra* is worldwide employed for ornamental purposes and takes the popular names of café-de-salão and cafesinho in Brazil [32]. As far as we know, no isolation work or ethnomedical use has ever been reported for it, whereas other *Leea* spp., like *L. guineense*, are popularly employed for treating hypertention [35]. Compounds isolated from the leaves of *L. guineense* include sulphate derivatives from quercetin (**4**), along with kaempferol, quercetin, quercitrin, mearnsitrin, gallic acid and ethyl gallate.

Similarly to the other active species here described, flavonoids can be hypothesized as the *in vitro* ACE inhibiting compounds from *L. rubra*. Quercetin (**4**), its derivatives and others flavonoids isolated from *L. guineense* might be regarded among the active compounds from *L. rubra*, supposing their presence in the species.

P. roebelinii is an exotic species in Brazil, where it is cultivated for ornamental purposes. The extract from its leaves produced a significant ACE inhibition (79.7±7.5%). Phytochemical studies, biological activities and ethnomedical uses have never been described for the species. On the other hand, the ethanolic extract from the leaves of *Phoenix sylvestris*, popularly employed in India as diuretic, produced 48 % of ACE inhibition, when assayed at the concentration of 0.33 mg/ml. After removing tannins from the extract, the authors reported only 8% of enzyme inhibition, suggesting the participation of compounds from this class in the biological activity [5].

Phoenix species have already been investigated and resulted in the isolation of several polysaccharides in particular from *P. dactylifera* seeds [36] and fruits [37]. Based on this finding, it can be speculated that polysaccharides might be responsible for the ACE inhibiting activity here described for *P. roebelinii*. The ACE inhibitory activity reported for hetero-chitoologosaccharides [38] is an additional evidence to support this proposition, though the ACE inhibitory mechanism of this class of compounds remains to be clarified.

Among the results here reported it should also be highlighted the activity observed for the Araliaceae *D. macrocarpum* and *S. actinophylla* and for the Cecropiaceae *C. glaziovii*. In fact, they presented ACE inhibition rates around 45% and should also be considered for further studies. The family Combretaceae also deserves further investigations, since it furnished two species with ACE inhibition rates above 50% (*C. fruticosum* and *T. catappa*). The occurrence of polyphenols, especially flavonoids, in particular quercetin (**4**), is a common feature in the ACE inhibiting species disclosed in the present work, or in other species from the same genera. The association between the regular intake of flavonoid-rich foods and a decreased risk of cardiovascular diseases is well documented by epidemiological studies [39]. Evidences that ACE inhibition can explain the health effect of flavonoids in general are given by the ability of ACE inhibitors to modulate anti-oxidant defenses and regulate mitochondrial NO production [40]. In this direction, it has been speculated that flavonoids may regulate anti-oxidant defenses through mechanisms that involve

ACE, highlighting the participation of flavan-3-ols and procyanidins in the modulation of oxidative stress, vascular function and cardiovascular disease [41].

In conclusion, our survey disclosed several plant species which are potential sources of angiotensin-converting enzyme inhibitors. Among the assayed species, the extracts of *C. brasiliense*, *C. fruticosum*, *L. rubra*, *P. roebelinii* and *T. catappa* produced significant ACE inhibition.

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