Promising Medicinal Plants with Diuretic Potential Used in Brazil: State of the Art, Challenges, and Prospects

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ABSTRACT

Medicinal plants are used in traditional medicine to treat a wide range of ailments. The knowledge of them is handed down from generation to generation and is described in several pharmacopoeia and in the general literature. The immense biodiversity of the Brazilian flora, covering about 25% of all plant species worldwide, makes Brazil a huge potential source of medicinal plants. Indeed, many of these plant species are already used in the Brazilian ethnopharmacology for their probable effect to induce diuresis, to reduce fluid retention, and to treat cardiovascular and renal disorders. This review article describes and discusses the main native Brazilian medicinal plants (including some of their isolated compounds) used as diuretics. It also gives a comprehensive analysis of the most relevant scientific studies presented to date, as well as addressing a special topic with future prospects for plant species that have not yet been scientifically studied. In brief, several plants can be indicated for more detailed study, with a view to obtain scientific subsidies for a new and effective diuretic medicine in the future. These include *Bauhinia forficata, Leandra dasytricha*, and *Tropaeolum majus*. Other species have reputed medicinal properties but lack experimental assays to demonstrate their pharmacological effects (*e.g., Mikania hirsutissima, Phyllanthus niruri, and Tagetes minuta*). Several active principles are indicated as responsible for the diuretic effects of the plants studied, with emphasis on phenolic compounds as flavonoids, phenolic acids, and xanthones. These results should encourage more detailed preclinical, clinical, and phytochemical investigations on Brazilian plants in the future.

Introduction

Natural products and their derivatives are very important in modern medicine. According to Newman & Cragg [1], more than 30% of the drugs approved worldwide between 1981 and 2019 came directly from natural sources, with emphasis on compounds obtained from medicinal plants. Medicinal plants are used in traditional medicine to treat a wide range of ailments. The knowledge of them is handed down from generation to generation and is described in several pharmacopoeia and in the general literature. The estimated global market for these drugs is worth around 400 million dollars a year [2].

The immense biodiversity of the Brazilian flora, comprising over 45,000 species and accounting for around a quarter of all plant species found worldwide, makes Brazil a potential source of medicinal and exotic plants [2–4]. The Brazilian population has a long history of the use of medicinal plants to treat various diseases, a practice that has been influenced by indigenous, African, and European cultures. These influences form the basis of Brazilian popular medicine [5, 6].

ABBREVIATIONS

ABTS	2,2′-Azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)
A7r5	aorta fibroblast
B2	bradykinin receptors
DPPH	2,2-diphenyl-1-picryl-hydrazil
DOCA	deoxycorticosterone acetate
HUVEC	human umbilical vein endothelial cells
IL-6	interleukin-6
L-NAME	N(ω)-nitro-L-arginine methyl ester
L929	murine fibroblast subcutaneous connective tissue
NTR	normotensive rats
Renisus	National List of Medicinal Plants of Interest to the Unified Health System
ROS	reactive oxygen species
SHR	spontaneously hypertensive rats
TCC	triterpene mix
TNF-α	Tumor Necrosis Factor-alpha
TTE	total triterpene extract

In 2009, the Ministry of Health of Brazil created a list of Medicinal Plants of Interest to the SUS (*Sistema Único de Saúde*) or Unified Health System, the Brazilian national healthcare system. This list known in Brazil as the Renisus, and it aims to guide and strengthen research on the species included in the list, especially native ones [7]. The list describes 71 species, including, for example, *Bauhinia forficata* Link, *Equisetum arvense* L., and *Maytenus ilicifolia* Mart. ex Reissek, which will be addressed in the course of this review due to their popular indication as diuretics.

Many medicinal plants, whether included in the Renisus list or not, are used in traditional Brazilian medicine for their possible diuretic actions [7–11]. Indeed, the Brazilian market offers many phytotherapeutic preparations to induce diuresis, sometimes containing a mixture of different plants or extracts and often without any experimental confirmation or approval from The Brazilian Health Regulatory Agency (Anvisa), an autarchy linked to the Brazilian Ministry of Health that is responsible for these processes. A preparation with diuretic properties should cause an increase in the volume and degree of urinary flow, as well as the elimination of electrolytes such as sodium and potassium. Such medicines are used to reduce fluid retention and as a form of treatment for different cardiovascular and renal disorders, such as renal failure, heart failure, liver cirrhosis, and, in particular, arterial hypertension [12]. Indeed, standard diuretics used in clinical treatment are the second most frequently prescribed class of medication to treat hypertension, with proven results in reducing disease-related morbidity and mortality [13].

In this review, we discuss the main native Brazilian medicinal plants (including some of their isolated compounds) used as diuretics, as well as offering a comprehensive analysis of the scientific studies published to date. We also address a special topic with future prospects for a species that has not yet been scientifically studied.

Material and Methods

The data collection for this review consisted of reports published from January 1989 to June 2020 in journals and books indexed online. Material was collected from ethnobotanical textbooks and scientific databases such as Pubmed (https://www.ncbi.nlm.nih.gov/pubmed), Science Direct (http://www. sciencedirect.com/), Medline (https://www.nlm.nih.gov/bsd/pmresources.html), and Google Scholar (https://scholar.google.com/). Original articles, some of them from the authors, reviews, experimental studies, and clinical approaches were considered.

Brazilian medicinal plants with diuretic potential

Several medicinal plants and their isolated compounds have been used as diuretic agents. The Brazilian medicinal plants popularly used to promote diuresis, as well as their isolated compounds when available, and for which there have been preclinical studies with proven efficacy, are shown in ▶ **Table 1**. The table gives the official name of each plant, the family, the part of the plant that was investigated in the studies (roots, stem, leaves, flowers, fruits, or whole plant), the type of extract and the active principles showing diuretic activity, the effective doses, the animal lineage used in the experiments, and the duration of experiment in hours or days.

Beginning our report with the medicinal plants included on the Renisus list [7], we describe the studies already published on the following species: *B. forficata* Link, *E. arvense* L., and *M. ilicifolia* Mart. ex Reissek. De Souza et al. [14] recently carried out a study with the leaves *of B. forficata*, commonly known as “pata-de-vaca” in Brazil and widely used for kidney disorders. The results demonstrated that the aqueous infusion of *B. forficata* leaves, at a dose of 300 mg/kg, was able to increase diuresis but not electrolyte excretion in NTR. On the other hand, the methanolic extract from the leaves showed an increase in urinary volume and electrolyte excretion at doses of 100 and 300 mg/kg. The fractions of chloroform and ethyl acetate plus butanol, obtained from methanolic extract, were also able to induce diuresis at doses of 100 mg/kg. This study also demonstrated that the flavonoid kaempferitrin appears to be the main component responsible for the diuretic effect found. *E. arvense,* known as “cavalinha”, is one of the few species whose effects have been evaluated in clinical studies, as described by Carneiro et al. [15], which confirmed its diuretic effect on healthy individuals. Tago et al. [16] evaluated the preclinical toxicity of *E. arvense* in the diet at concentrations of 0.3%, 1%, and 3% for 13 wk in male and female rats. The results demonstrated that there were no signs of toxicity in relation to clinical signs, body weight, biochemical urine and blood tests, organ weight, and histological analysis. However, we cannot rule out possible adverse effects from the use of this plant, as they have not yet been studied in clinical trials. The last plant on the Renisus list that is popularly used for diuresis is *M. ilicifolia*, popularly known as “espinheira santa”, which is native to southern Brazil and is popularly used for kidney disorders. Studies have shown that the ethyl acetate fraction obtained from the infusion of *M. ilicifolia* leaves in water had diuretic and natriuretic effects at doses of 30 and 100 mg/kg in NTR [17].

▶ **Table 1** Evidence of preclinical studies reporting diuretic effect of extracts and isolated compounds obtained from Brazilian medicinal plants. NTR: normotensive rats; SHR: spontaneously hypertensive rats. *ne*: not effective.

Species	Family	Plant part	Type of extract/ isolated compound	Effective dose	Time of experiment	Animal model	Reference
Alibertia edulis (Rich.) A.Rich. ex DC.	Rubiaceae	Leaves	Aqueous	200 mg/kg	8 h and 7 days	NTR and SHR	[34]
			Ethyl acetate	100 and 400 mg/kg	6 h	NTR	
			Butanolic	12.5, 25, and 50 mg/kg	6 h	NTR	
			Triterpene-enriched extract	5, 20, and 40 mg/kg	6 h	NTR	
Anchietea pyrifolia (Mart.) G.Don	Violaceae	Leaves	Ethanolic	30 mg/kg	8 h and 7 days	NTR	[39]
Bauhinia forficata Link	Leguminosae	Leaves	Aqueous	300 mg/kg	8 h	NTR	[14]
			Methanolic	100 and 300 mg/kg	8 h	NTR	
			Chloroform	100 mg/kg	8 h	NTR	
			Ethyl acetate + Butanol	100 mg/kg	8 h	NTR	
			Kaempferitrin	0.3 and 1 mg/kg	8 h	NTR and SHR	
Cissampelos parreira L.	Menispermaceae	Roots	Ethanolic	100, 200, and 400 mg/kg	5 h	NTR	[31]
Echinodorus grandiflorus (Cham. & Schltdl.) Micheli	Alismataceae	Leaves	Aqueous	300 mg/kg	7 days	NTR	[30]
Garcinia achachairu Rusby	Clusiaceae	Branches	Methanolic	10 and 30 mg/kg	8 h	NTR	[41]
			Ethyl acetate	1, 3, and 10 mg/kg			
			Dichloromethane	1, 3, and 10 mg/kg			
			Butanolic	10 mg/kg			
			1,3,5,6-tetrahydroxy-xanthone	0.1 and 0.3 mg/kg			
			(−)-epicatechin	0.3, 1, and '3 mg/kg	8 h	NTR and SHR	[48]
Gomphrena celosioides Mart.	Amaranthaceae	Aerial	Ethanolic	100 mg/kg	8 h and 7 days	NTR	[33]
Leandra dasytricha (A. Gray) Cogn.	Melastomataceae	Leaves	Ethyl acetate	10 and 30 mg/kg	8 h	NTR	[36]
			Nothofagin	1 mg/kg	8 h	NTR and SHR	[36, 80]
Luehea divaricata Mart.	Malvaceae	Leaves	Aqueous	30, 100, and 300 mg/kg	8 h and 7 days	NTR	[37]
			Butanolic	65 mg/kg	8 h, 24 h, and 7 days	NTR	[38]
Marlierea eugeniopsoides (D.Legrand & Kausel) D.Legrand	Myrtaceae	Leaves	Methanolic	10–100 mg/kg	8 h	NTR	[42]
			Dichloromethane	10 and 30 mg/kg			
			Ethyl acetate	10 and 30 mg/kg			
			Myricitrin	0.3 and 1 mg/kg	8 h		
			Myricitrin	0.3 mg/kg	24 h		
Maytenus ilicifolia Mart ex Reissek	Celastraceae	Leaves	Ethyl acetate	30 and 100 mg/kg	8 h	NTR	[17]
Mimosa bimucronata (DC.) Kuntze.	Leguminosae	Leaves	Methanolic	30 and 100 mg/kg	8 h	NTR	[43]
			Methyl gallate	1 and 3 mg/kg	8 h	NTR and SHR	
			Gallic acid	3 mg/kg	8 h and 24 h	NTR	[71]

cont.

▶ **Table 1** *Continued*

Species	Family	Plant part	Type of extract/ isolated compound	Effective dose	Time of experiment	Animal model	Reference
Mimosa pudica L.	Leguminosae	Whole plant	Ethanolic	200 mg/kg	5 h	NTR	[24]
			Aqueous	200 mg/kg	5 h	NTR	
		Root	Ethanolic	100 and 200 mg/kg	5 h	NTR	[25]
Palicourea coriacea (Cham.) K Schum.	Rubiaceae	Aerial	Ethanolic	20, 40, and 8 mg/kg	8 h	NTR	[26]
Pereskia grandifolia Haw.	Cactaceae	Leaves	Ethanolic	30 mg/kg	8 h and 7 days	NTR	[18]
Phyllanthus amarus Schumach. & Thonn.	Phyllanthaceae	Leaves	Ethanolic	80 mg/kg	8 h	NTR	[94]
Piper amalago L.	(Piperaceae)	Leaves	Ethanolic	125, 250, and 500 mg/kg	24 h	NTR	[23]
P. glabratum (Kunth) Steud.	(Piperaceae)	Roots	Methanolic	*ne*	8 h	NTR	[22]
			2-methoxy4,5-methylenedioxy-*trans*-cinnamoyl-pyrrolidine	30 mg/hg			
Rudgea viburnoides (Cham.) Benth.	Rubiaceae	Leaves	Ethanolic	40, 80, and 160 mg/kg	8 h	NTR	[29]
Scutia buxifolia Reissek	Rhamnaceae	Barks	Hydroethanolic	30 and 100 mg/kg	8 h	NTR	[28]
			Butanolic	3 and 10 mg/kg	8 h	NTR	
Talinum paniculatum (Jacq.) Gaertn.	Portulacaceae	Leaves	Ethanolic	30, 100, and 300 mg/kg	7 days	NTR	[40]
Tropaeolum majus L.	Tropaeolaceae	Leaves	Ethanolic	300 mg/kg	8 h and 7 days	NTR	[19, 20]
			Hydroethanolic	3, 30, and 300 mg/kg	4 weeks	NTR	[21]
			Isoquercitrin	10 mg/kg	7 days	SHR	[66]

There are some species of plants that, in addition to medicinal use as diuretics, are also known for their culinary uses, including *Pereskia grandifolia* Haw. and *Tropaeolum majus* L. The ethanolic extract obtained from the leaves of *P. grandifolia*, known as "rosa-madeira" or "American beech", was tested in preclinical studies by Kazama et al. [18]. The results obtained in male and female NTR indicated that the ethanolic extract was able to increase the urinary volume at a dose of 30 mg/kg in 8 h of the experiment, as well as decreasing the urinary excretion of K^+ and Cl^-. The authors also evaluated the infusion of leaves obtained from *P. grandifolia* but found that no concentration was able to increase the volume of urine in 8 h of the experiment. The experiment was also carried out with 7 days of treatment with ethanolic extract of *P. grandifolia*, and it was found that the dose of 30 mg/kg also increased the volume of urine. Despite this, the ethanolic extract of *P. grandifolia* leaves did not alter Na^+ excretion, an effect that would be expected for a diuretic, although it did alter other electrolytes, which is also of great biological interest. Those researchers also found that the mean arterial pressure of animals treated with ethanolic extract at a dose of 30 mg/kg was lower than that of the control group (treated with water only). They also measured serum vasopressin levels, which they found to be reduced in the presence of the extract. According to Gasparotto et al. [19], the aqueous infusion with the leaves of *T. majus*, popularly known as "chaguinha", at a dose of 500 mg/kg, was able to increase urinary Na^+ excretion in NTR but did not alter the volume of urine. They also extracted *T. majus* leaves with ethanol and found that the dose of 300 mg/kg obtained good results for electrolyte excretion and was able to induce an increase in urine volume of NTR in experiments conducted for 8 h, over a period of 7 days of treatment. The authors also demonstrated that the ethanolic extract increased diuresis similarly to spironolactone, a conventional K^+-sparing diuretic, an effect that they associated with decreased plasmatic aldosterone levels [20]. Extending the studies on this plant, Barboza et al. [21] evaluated the effect of hydroethanolic extract of *T. majus* leaves at doses of 3, 30, and 300 mg/kg in ovariectomized rats over a 4-wk period to determine whether long-term treatment with the extract would impact on the presence of low levels of estrogen. The results of that study demonstrated that *T. majus* extract was able to sustain its diuretic effect after 4 wk of treatment and did not affect the urinary excretion of Ca^{2+} and K^+, confirming the potential of the extract as a

candidate for use in clinical conditions such as osteoporosis, in which renal loss of Ca^{2+} is not desired. The abovementioned authors also demonstrated that the isolated compound isoquercitrin seems to be the main compound responsible for the diuretic effect found.

The genus *Piper*, popularly known as "falso-jaborandi" or "pepper plant", has been extensively studied for its potential pharmacological use, due to the presence of promising secondary metabolites. Among the biological effects and the popular use of the genus, the diuretic effect is highlighted [22]. Two species were the subject of more detailed experimental study to assess the possible diuretic effect: *P. amalago* L. and *P. glabratu*m (Kunth) Steud. According to Novaes et al. [23] the ethanolic extract of *P. amalago* leaves showed a diuretic effect at doses of 125, 250, and 500 mg/kg, associated with increased excretion of Na^+ and K^+ in the urine of NTR. Prando et al. [22] investigated the effects of the methanolic extract of the roots of *P. glabratum* and the 2-methoxy4,5-methylenedioxy-*trans*-cinnamoyl-pyrrolidine compound isolated from the extract. However, the compound only showed significant diuretic effect at the dose of 30 mg/kg.

The *Mimosa* genus has also been the subject of studies to determine the possible diuretic effect of one of its species: *M. pudica* Linn, known as "dormideira" in Brazil and by numerous common names in English, including "sensitive plant", "humble plant", "shameplant", and "touch-me-not". Baghel et al. [24] evaluated the diuretic effect of its aqueous and ethanolic extract in albino rats. The animals were orally treated with extract obtained from whole plant at doses of 100 and 200 mg/kg. The urine volume was measured after 5 h of treatment, showing an increase in relation to the control group (at a dose of 200 mg/kg). Interestingly, the dose of 200 mg/kg also increased the excretion of Na^+, K^+, and Cl^-, confirming that the effect of this extract is not only aquaretic but also diuretic. Another study of diuresis using *M. pudica* was conducted by Kalabharathi et al. [25], who used ethanolic extract of the roots to evaluate the diuretic effect in albino rats. In their 5 h experiment, animals received the extract orally at doses of 100, 200, and 400 mg/kg. An increase in urine was observed at all doses, but only the doses of 100 and 200 mg/kg were able to increase the excretion of Na^+ and Cl^- in the urine, thus presenting a saluretic effect, which would be expected of a diuretic medication. On the other hand, all doses were able to increase the excretion of K^+ in the urine, an effect that would also be expected from a diuretic, except when it comes to K^+-sparing diuretics.

Palicourea coriacea (Cham.) K Schum., popularly known as "douradinha-do-campo" and found in the Midwest of Brazil, has been widely used for kidney disorders [26]. Although the aerial parts of this plant are commonly used in the form of aqueous preparations for diuresis, there are only a few reports proving their effect in experimental studies. According to Freitas et al. [26], the ethanolic extract of the aerial parts of this plant showed a diuretic effect at doses of 20, 40, and 80 mg/kg, as well as an increase in the excretion of Na^+ and K^+ in NTR. On the other hand, the ethanolic extract at the dose of 2000 mg/kg did not present toxicity over a 14-day period of daily treatment in NTR, opening up prospects for prolonged pharmaceutical use of this plant.

In Brazil, *Scutia buxifolia* Reissek, commonly known as "coronilha", has also been widely used for diuresis [27]. Da Silva et al. [28] reported the diuretic effect of the hydroethanolic extract of the bark and the butanolic fraction obtained from the extract in NTR. The extract at the dose of 30 and 100 mg/kg was able to increase urinary volume after the second hour of treatment, whereas the butanolic fraction increased urinary volume at the dose of 10 mg/kg. Another species used in Brazilian traditional medicine as a diuretic agent is *Rudgea viburnoides*, popularly known as "congonha-de-bugre". Pucci et al. [29] conducted a study demonstrating the diuretic effect of the crude ethanolic extract of the leaves and demonstrated an interesting effect at doses 40, 80, and 160 mg/kg, with increased excretion of urine and electrolytes in NTR.

Another species that deserves mention is *Echinodorus grandiflorus* (Cham. & Schltdl.) Micheli, known as "chapéu-de-couro", also used in folk medicine due to its reputed diuretics properties. Prando et al. [30] demonstrated that the aqueous extract of *E. grandiflorus* leaves, in 7 days of treatment, increased the volume of urine at a dose of 300 mg/kg from the second day of treatment when compared to the negative control group. In addition, the dose of 300 mg/kg was also able to increase the excretion of Na^+ and K^+.

Cissampelos pareira L., commonly known as "abuta" or "velvetleaf", is another plant that is widely used in traditional medicine as a diuretic [10]. Sayana et al. [31] evaluated the diuretic effect of the ethanolic extract of the roots of this plant in NTR at oral doses of 100, 200, and 400 mg/kg, and found that a single administration of the extract increased the volume of urine after 5 h of experiment, an effect that was accompanied by increased excretion of Na^+, K^+, and Cl^-, confirming the diuretic and saluretic effect of the extract. There are reports in the literature regarding its acute toxicological profile (14 days) in mice and subacute toxicological profile (28 days) in rats, where the animals received a hydroethanolic extract of the roots obtained from *C. pareira* orally at a dose of 1 or 2 g/kg. The results revealed that the extract did not cause mortality or changes in the animals' behavior, being considered safe, but chronic toxicity studies are still needed to support the safe and healthy use of this plant [32].

Gomphrena celosioides Mart., known as "perpétua" in Brazil and "globe amaranth" or "bachelor's button" in English, is a native plant of Mato Grosso do Sul (Brazil), where it is used by the population to treat urinary tract disorders. De Paula Vasconcelos et al. [33] evaluated the ethanolic extract of its aerial parts in a diuresis model using NTR. The extract was administered orally at doses of 30, 100, or 300 mg/kg, and the volume of urine was measured for an experimental period of 8 h. The doses of 100 and 300 mg/kg were able to induce diuresis, accompanied by increased Na^+ excretion, when compared to the control group. Only the dose of 300 mg/kg was able to increase the excretion of K^+ and Cl^-, and none of the treatments altered the urinary excretion of Ca^{2+}. In the same study, the authors evaluated the possible mode of action of the extract, detecting an effect that was dependent on the nitric oxide pathway, prostaglandins, and bradykinins, based on the finding that pretreatment with the inhibitors of each pathway reduced the diuretic effect of the extract. They also conducted a prolonged diuresis experiment and found that the effect of the extract at a dose of 100 mg/kg was maintained for the

7 days of daily treatment. Following a similar approach, a decoction of *Alibertia edulis* (Rich.) A.Rich. ex DC., known as "marmelinho" in Brazil or "wild guava" in English, and used in Brazilian folk medicine to treat hypertension, was evaluated to determine its possible diuretic effect. The extract, at dose of 200 mg/kg, increased the volume of urine, as well as the urinary excretion of Na^+, K^+, Cl^-, and Ca^{2+} in 8 h and 7 days of treatment [34]. These results confirm the popular use of this plant and open up prospects for its use in other cardiovascular disorders. Menegati et al. [35] evaluated the safety of the aqueous extract of *A. edulis* leaves in a model of acute toxicity (14 days of treatment) at a dose of 2000 mg/kg and subchronic toxicity (28 days of treatment) in different doses, in male and female NTR. The results did not indicate any signs of toxicity or behavioral changes. Although the extract was considered safe in a preclinical model, additional assessments are still needed before clinical trials can be conducted.

An approach of diuresis assay after 8 h of treatment was conducted by our research group, confirming the diuretic effect of the ethyl acetate fraction obtained from the methanolic extract of the leaves of *Leandra dasytricha* (A. Gray) Cogn., known as "pixirica", a plant popularly used in Brazil to treat kidney disorders. The results obtained showed that the fraction of ethyl acetate did not modify the excretion of electrolytes in the urine but was able to promote aquaresis at doses of 10 and 30 mg/kg. This study also demonstrated that the majority isolated compound of this plant, known as nothofagin, had diuretic and natriuretic effects at low doses in both NTR and SHR [36].

We could not describe the use of plants as diuretics without mentioning *Luehea divaricata* Mart., popularly known in Brazil as "açoita-cavalo", which is widely used in folk medicine to treat various several ailments. Tirloni et al. [37] demonstrated the diuretic effect of the aqueous extract obtained from the leaves of *L. divaricata* at doses of 30, 100, and 300 mg/kg in female and male NTR, as well as its effect on blood pressure of male NTR. After 8 h and 7 days of treatment, the aqueous extract was able to induce diuresis and saluresis in the animals. Mean and systolic blood pressure were reduced after acute treatment with the aqueous extract of *L. divaricata*. Additionally, the results obtained after 7 days of the experiment led to the conclusion that the diuretic and hypotensive results of *L. divaricata* are probably related to a reduction in oxidative stress and an increase in nitric oxide bioavailability. A subsequent study evaluated the diuretic effect of the aqueous extract and the fractions of ethyl acetate and butanolic fractions from the leaves of *L. divaricata* in male NTR. Only the butanolic fraction at the dose of 65 mg/kg showed diuretic and saluretic effects at 8 h, 24 h, and 7 days of treatment, as well as increased serum nitrite levels and reduced oxidative markers. The butanolic fraction also showed sustained hypotensive effect and was able to cause vasodilation in the renal and peripheral arteriolar bed by releasing nitric oxide and prostaglandins [38].

The last 2 plants of this topic of the review were recently evaluated for their diuretic effect in animal models: *Anchietea pyrifolia* (Mart.) G.Don [39] and *Talinum paniculatum* (Jacq.) Gaertn. [40]. The diuretic activity of the leaves of *A. pyrifolia*, known in Brazil as "cipó-do-mato", was investigated by Tolouei et al. [39] in male and female NTR. The results found in 8 h and 7 days of treatment showed that the leaf extract, at a dose of 30 mg/kg, had diuretic and saluretic effects after 7 days of treatment. This study also demonstrated the hypotensive effect of the extract of *A. pyrifolia* after prolonged use and found no signs of toxicity during and after treatment with the leaf extract. Finally, the diuretic and hypotensive activity of *T. paniculatum*, known in Brazil as "caruru", was demonstrated by Tolouei et al. [40] in male NTR. The results of that study showed that the ethanol fraction of the oil obtained from the leaves of *T. paniculatum* after 7 days of treatment in different doses (30, 100, and 300 mg/kg) had diuretic and saluretic effects but did not alter blood pressure or heart rate.

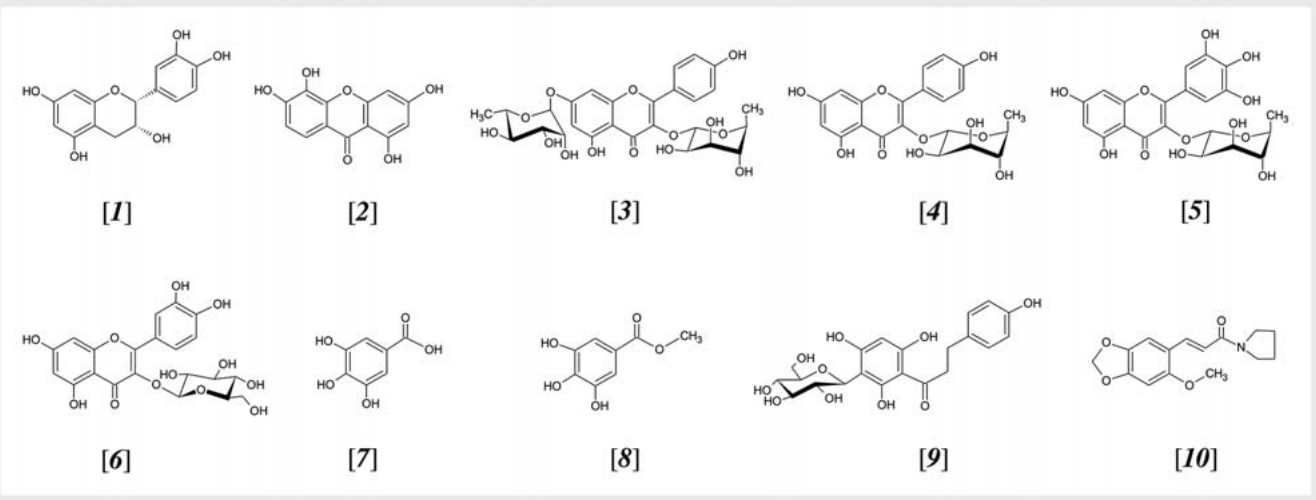
Other Brazilian medicinal plants of interest with reported diuretic activity

Some Brazilian plants, despite being used in traditional medicine for purposes other than diuretics, have been submitted to biological tests by our research group, mainly due to their wide geographical distribution and the variety of chemical compounds in their composition: *Garcinia achachairu* Rusby [41], *Marlierea eugeniopsoides* (D.Legrand & Kausel) D.Legrand [42], and *Mimosa bimucronata* (DC.) Kuntze [43].

The diuretic activity of branches of *G. achachairu*, popularly known as "achachairu", was investigated using the acute diuresis model (8 h) in female NTR. The methanolic extract showed diuretic activity at doses of 10 and 30 mg/kg accompanied by a decrease in urinary excretion of K^+ and an increase in Cl^-. On the other hand, the dichloromethane and ethyl acetate fractions obtained from the extract increased urinary excretion at all doses tested (1, 3, and 10 mg/kg), while only the dose of 1 mg/kg of the ethyl acetate fraction showed a saluretic effect. The butanol fraction showed a diuretic effect only at the dose of 10 mg/kg, accompanied by an increase in urinary Cl^- excretion. The authors suggest that the differences found are related to the chemical constituents (composition and quantity) of the fractions. This study also demonstrated that the isolated compounds 1,3,5,6-tetrahydroxyxanthone and (−)-epicatechin appear to contribute significantly to the diuretic effect found [41].

Regarding *M. eugeniopsoides*, known as "guamirim", Tenfen et al. [42] evaluated the diuretic effect of the extract and fractions of the leaves. The results showed that the methanolic extract increased the volume of urine at doses of 10, 30, and 100 mg/kg in NTR after 8 h of treatment. Moreover, the dichloromethane and ethyl acetate fractions were able to increase the volume of urine at doses of 10 and 30 mg/kg. The fraction of dichloromethane, at a dose of 30 mg/kg, increased urinary K^+ excretion. This study also demonstrated that the isolated compound myricitrin seems to be the main compound responsible for the diuretic effect found.

Experimental studies conducted by our laboratories revealed that *M. bimucronata*, known as "espinheira", exhibited promising diuretic effect in male NTR that received, orally, methanolic extract and the dichloromethane and ethyl acetate fractions from the leaves of the plant. The extract, at doses of 30 and 100 mg/kg, was able to increase the volume of urine in relation to the negative control group. On the other hand, only the fraction of ethyl acetate, at the dose of 30 mg/kg, was able to increase the volume of urine, which suggests that the type of chemical constituent that the solvent ethyl acetate is capable of extracting is habitually a fraction rich in flavonoids. Interestingly, the extract was able to



▶ **Fig. 1** Structure of the compounds obtained from Brazilian medicinal plants tested with respect to their diuretic effects. (***1***) (−)-epicatechin; (***2***) 1,3,5,6-tetrahydroxyxanthone; (***3***) kaempferitrin; (***4***) afzelin; (***5***) myricitrin; (***6***) isoquercitrin; (***7***) gallic acid; (***8***) methyl gallate; (***9***) nothofagin; (***10***) 2-methoxy4,5-methylenedioxy-*trans*-cinnamoyl-pyrrolidine.

increase the excretion of Na^+ at all doses and of K^+ only at the dose of 100 mg/kg. This study also demonstrated that the isolated compounds methyl gallate and gallic acid appear to be the main compounds responsible for the diuretic effects described in the study [43]. Indeed, we can see the promising potential of these Brazilian species for diuretic purposes, stimulating studies on other plants in popular use that, although not yet scientifically investigated, may present chemical constituents of interest and with high therapeutic value.

Isolated compounds from Brazilian medicinal plants with diuretic potential

Bioactive constituents of plants, especially alkaloids, terpenes, and phenolic compounds, have long been investigated as rich sources of agents for medicinal use [44, 45]. The structure of the compounds obtained from Brazilian medicinal plants tested with respect to their diuretic effects are displayed in ▶ **Fig. 1**. Flavonoids, for instance, have been proven to prevent or attenuate cardiac and renal injuries associated with hypertension by interfering with the multiple signaling pathways [46]. One such flavonoid of interest is (−)-epicatechin [1], which is abundant in several plants and food products, including cocoa, green tea, juice, and wine. According to the literature, this compound can be beneficial for human health, including in cardiovascular disorders [47]. This compound has been isolated from branches of *G. achachairu* and explored its role in acute diuresis in both NTR and SHR. The results showed that it was able to enhance diuresis, associated with an increase in Na^+, K^+, and Cl^- excretion at different doses (0.3–3 mg/kg). Also, the treatment did not affect plasma electrolyte content, urinary pH, or uric acid values. When the compound (1 mg/kg) was associated with the well-known thiazide diuretic hydrochlorothiazide (10 mg/kg), the ***1***-diuretic effect was intensified. Regarding the possible mechanism of diuresis involved, we observed that urinary excretion was improved after pretreatment with L-NAME, and that its action was significantly precluded in the presence of a cyclooxygenase inhibitor (indomethacin), suggesting that the diuretic role of ***1*** may involve endogenous vasodilator mediators [48]. The protective cardiovascular role of ***1*** was also demonstrated in other models. Jackson et al. [49] investigated the effects of 28 days of treatment with ***1*** (1 mg/kg) in DOCA-salt in hypertensive rats and found that epicatechin was able to reduce blood pressure, prevent myocardial stiffening, and preserve cardiac compliance. MacRae et al. [50] studied the possible mechanism of action of ***1*** in cardiovascular vasorelaxation using isolated rat arteries and resistance vessels. The authors suggested that the vasorelaxation caused by ***1*** may be mediated through the opioid receptors, nitric oxide, potassium channel, and calcium channel activation. Concerning its safety, when ***1*** was given to humans in different doses, it proved to be safe with no observed adverse effects [51]. We also considered a xanthone isolated from *G. achachairu* branches in our lab [41], identified as 1,3,5,6-tetrahydroxyxanthone [2]. Xanthones are a class of polyphenolic compounds that are widely found in plants and present beneficial cardiovascular effects. For instance, they play an important role in ischemic heart disease, atherosclerosis, hypertension, and thrombosis. Their potential may be related to their antioxidant, anti-inflammatory, platelet aggregation inhibition, antithrombotic, and vasorelaxant activities [52]. Some authors have demonstrated the role of xanthones and their derivatives in the cardiovascular system, as anti-arrhythmics, hypotensive [53], and anti-aggregations agents [54], for example. We have investigated the role of ***2*** in 8 h and 24 h diuresis in both NTR and SHR. At a dose of 0.1 mg/kg, ***2*** induced diuresis in both models, associated with enhanced Na^+ and K^+ urinary elimination. Also, Ca^{2+} excretion was decreased in the 24 h experimental period after treatment with ***2***. Its combination with furosemide or hydrochlorothiazide resulted in an increase in urinary volume. Furthermore, ***2***-induced diuresis was enhanced after pretreatment with L-NAME, and its ability to enhance urinary elimination was not prevented in the presence of either indomethacin or atropine [41].

Kaempferitrin [3] (kaempferol 3,7-dirhamnoside), a kaempferol-derived flavone found in some plant species, is the main chemical compound of *B. forficata* leaves and is related to the pharmacological activity of this species [55, 56]. This compound was also investigated in our laboratories, focusing on its acute diuretic effects, in a preclinical model using both NTR and SHR at doses ranging from 0.1 to 1 mg/kg. It was observed that ***3*** presented potent effect, inducing diuresis in both NTR (0.3 and 1 mg/kg) and SHR (1 mg/kg). The treatment did not affect the pH, density, or conductivity parameters. Furthermore, ***3*** treatment increased Na^+ excretion, and the highest dose in NTR showed a K^+-sparing activity, suggesting that ***3*** presents diuretic and natriuretic but not kaliuretic action. The possible mechanism of action was investigated, and it was proposed that ***3***-induced diuresis is independent of nitric oxide generation or muscarinic receptor activation but is related to endogenous prostanoid generation [14]. We also investigated the role of kaempferitrin in vasorelaxation in NTR and SHR aortic rings, and both ***3*** and its aglycone, kaempferol (0.001–0.3 µg/mL), were able to induce vasorelaxation by 34.70% and 40.54%, respectively [57]. There have been few studies on the toxic potential of this compound, but *in vitro* investigations have shown that despite being cytotoxic to cancer cell lines [58], kaempferitrin did not exert any toxicity in intestinal epithelial cells (IEC-6 lineage) [59].

It is important to note that when kaempferitrin is metabolized, it is biotransformed into at least 2 other active metabolites, as afzelin [4] and kaempferol [60]. For this reason, we also evaluated the diuretic and renal protective effects of these 2 compounds in NTR and SHR. It is important to emphasize that ***4*** presented an acute and prolonged diuretic effect at a very low dose (0.1 mg/kg), with endogenous prostanoid generation and muscarinic receptor activation being linked to its mode of action. In addition, ***4*** induced an increase in urinary Na^+ and Cl^- excretion and a decrease in Ca^{2+} elimination. It was also able to decrease ROS and nitrite generation in the kidneys. Moreover, ***4*** was able to significantly reduce calcium oxalate crystal formation in the urine, with inhibition rates of 41% for NTR and 92% for SHR. This study also demonstrated that ***4*** attenuates renal damage in SHR, evidenced by the thickness of the Bowman's capsule and the organization of the glomerular mesangial flow. However, its aglycone kaempferol was not effective at any of the doses tested, suggesting that the glycosylated forms, ***3*** and its derivative ***4***, depend on their glycosylated portions to obtain renal effects [61].

Another important flavonoid, which is common in plant species, is myricitrin [5]. This is a glycosyloxyflavone that consists of myricetin attached to an alpha-L-rhamnopyranosyl residue. Several studies have demonstrated its role in cardioprotection. For instance, it is able to modulate the expression of adhesion molecules, which is important in the pathogenesis of atherosclerosis [62]. It also protects H9c2 cardiomyocytes against hypoxia/reoxygenation-induced oxidative stress and apoptosis [63]. It is also considered a safe flavonoid for use in food and beverages, without evidence of genotoxicity in animal research [64]. We have also isolated ***5*** from *M. eugeniopsoides* leaves and investigated its effect in urinary parameters in NTR. Myricitrin was able to induce diuresis, natriuresis, and kaliuresis when given orally to rats at doses of 0.3 and 1 mg/kg. However, it is important to emphasize that all groups treated with ***5*** showed a significant reduction in urinary Cl^- excretion and HCO_3^- after 24 h of treatment, a result that was shown to be linked to an increase of both Cl^- and HCO_3^- in the blood samples of the ***6***-treated group. The authors argue that changes in the excretion of Cl^- and HCO_3^- may be related to changes in the acid-base balance. Nevertheless, despite these alterations, no changes in urinary or blood pH were detected [42].

Isoquercitrin [6] (quercetin-3-O-glucoside) is a quercetin glucoside flavonoid that occurs naturally in medicinal plants, vegetables, and fruits. It is a compound that can also be obtained through rutin hydrolysis. It is important to state that it exerts higher availability and water solubility when compared to its aglycone form, quercetin. Several preclinical studies have demonstrated its beneficial effects against oxidative stress and cardiovascular disorders, and intake of up to 5 mg/kg/day of isoquercitrin is acceptable [65]. Gasparotto Junior et al. [66] investigated the effects of ***6*** isolated from *T. majus* in an acute and prolonged (7 days) diuresis model in SHR, at oral doses of 5 and 10 mg/kg. They found that ***6*** increased urine and Na^+ excretion in a dose-dependent matter, without affecting the other urinary parameters, such as pH, conductivity, and K^+ elimination. Also, Na^+ and K^+ levels in the plasma did not change after administration of ***6***, and no evidence of renal toxicity or other adverse effects was found. Gasparotto Junior et al. [67] also demonstrated that ***6***, given intravenously, was able to induce hypotension in rats, an effect that was linked to the reduction of angiotensin II generation, through its ability to inhibit the angiotensin-converting enzyme. Other studies have also evidenced its role in cardioprotection, (e.g., it induced vasodilatation in the resistance arteries of the rats, via K^+ channel opening and endothelial nitric oxide production) [68]. Moreover, a clinical trial showed that enzymatically modified ***6*** also enhanced endothelial functions in volunteers at risk of cardiovascular diseases [69].

Another compound with promising diuretic potential is gallic acid [7], a well-known natural phenolic bioactive found in distinct medicinal plants and fruits, with several health-promoting effects. It exhibits antioxidant, anti-inflammatory, and antineoplastic properties, with therapeutic properties in several disorders including those related to the cardiovascular system [70]. As reported by Schlickmann et al. [71], ***7***, isolated from *M. bimucronata*, was able to induce diuresis and saluresis (i.e., increased Na^+ and Cl^- levels in the urine) when given orally to NTR at a dose of 3 mg/kg. No effect on K^+ elimination or urinary pH values were observed. When ***7*** was associated with amiloride (3 mg/kg), a well-known potassium-sparing diuretic, its diuretic and saluretic effects were amplified. The authors also analyzed the possible pathway involved in this activity, showing that the diuretic action was significantly prevented in the presence of a cyclooxygenase inhibitor but not by pretreatments with L-NAME or atropine, suggesting the involvement of endogenous prostanoid generation in the renal effects evoked by this compound. This importance of this compound in cardiovascular protection has also been demonstrated in other experimental models. Jin et al. [72], for example, observed that ***7*** also had positive effects on cardiac dysfunction and fibrosis in a mouse model of pressure overload-induced heart failure, demonstrating its potential as therapeutic agent for cardiac dysfunction and fibrosis in chronic heart failure. Jin et al.

[73] also evidenced that **7** was able to attenuate cardiac hypertrophy and apoptosis in an essential hypertension rat model, suggesting that it may be considered as a novel therapeutic option for hypertension. Additionally, **7** can exert beneficial effects on cardiovascular models and health in general, and it is considered safe with a stable profile [70]. Ferk et al. [74] evaluated an intervention using **7** (15 mg/day) in diabetic patients. After 7 days, there was a significant reduction in oxidized purines (31%), plasma concentrations of oxidized-LDL (24%), and C-reactive protein (39%), showing that gallic acid prevents oxidative DNA damage and reduces markers of inflammation and increased risk of cardiovascular diseases.

Methyl gallate [8], a methyl ester of gallic acid, is another phenolic compound widely distributed in nature with high antioxidant potential, as well as anti-inflammatory, antimicrobial, and antitumor activities, described in the literature [75, 76]. Schickmann et al. [43] isolated **8** from *M. bimucronata* leaves and evaluated its single-dose potential to induce diuresis. It displayed diuretic, natriuretic, and kaliuretic properties in NTR (3 mg/kg) and SHR (1 and 3 mg/kg). According to the authors, atropine pretreatment fully inhibited **8**-induced diuresis and saluresis, suggesting activation of the muscarinic acetylcholine receptors. The authors also investigated the effects of **8** in A7r5 and L929 cell lines at different concentrations (0.3–30 µg/ml). The results showed that **8** did not demonstrate cytotoxic effects. Khurana et al. [77] observed that **8** was able to preserve the viability of neonatal rat cardiomyocytes exposed to H_2O_2 by decreasing intracellular ROS, maintaining mitochondrial membrane potential, augmenting endogenous glutathione, and reducing apoptosis. Whang et al. [75] described that **8** was able to protect HUVEC from oxidative stress. Taken together, these findings suggest a relevant therapeutic value for **8** in renal and cardioprotection.

Natural and synthetic chalcones have shown potential as candidates to prevent and treat various cardiovascular diseases, such as hypertension and arrhythmia, and are valuable for the discovery of new medicinal agents [78]. In this context, we have isolated the dihydrochalcone nothofagin [9] from *L. dasytricha* leaves and investigated its diuretic potential in both NTR and SHR at different doses (0.3–3 mg/kg). We found that **9** was able to induce diuresis and natriuresis but not kaliuresis. Also, **9** did not present toxic effects in L929 or A7r5 cell lines and was able to stimulate nitric oxide generation in A7r5 cells. Moreover, **9** demonstrated antioxidant effects in scavenging the free-radical DPPH. The results of the abovementioned study also showed that **9** induces diuresis, an effect associated with prostanoid generation, muscarinic receptor activation, and antioxidant properties [36]. Snijman et al. [79] also demonstrated the antioxidant potential of **9** using ABTS radical cation, considered a potent radical scavenger (IC_{50} = 4.04 µM). We also evaluated the dose-repeated effects of nothofagin at 1 mg/kg [80]. After 7 days of treatment, it was observed that **9** was able to induce prolonged diuretic effects in both NTR and SHR. These results were associated with increased levels of Na^+ and Cl^- in the urine. It is important to mention that no changes in K^+ excretion or other urinary or plasma parameters were identified. Moreover, daily treatment with **9** was able to restore the reduced glutathione levels and superoxide dismutase activity, 2 important endogenous antioxidant defenses, and to reduce lipoperoxidation in kidney homogenates obtained from SHR. Finally, **9** increased the levels of nitrite, a marker of nitric oxide production, in the plasma obtained from SHR when compared with vehicle-treated only NTR, suggesting that **9** may present the ability to modulate kidney function, which would benefit the entire cardiovascular and kidney system. Interestingly, Yang et al. [81] also evidenced renal protective potential of **9** against sepsis-triggered renal injury by decreasing the plasma levels of nitric oxide, cytokines (TNF-α and IL-6), and the myeloperoxidase enzyme (commonly associated with neutrophil infiltration). It also markedly enhanced the antioxidant defense system by restoring the levels of superoxide dismutase, glutathione peroxidase, and catalase in the kidney tissues. Another 2 recent studies have expanded the therapeutic possibilities of **9**; according to Marques et al. [82], the compound (30, 100, and 300 nmol) induced endothelium-dependent and dose-dependent vasodilation in the renal arteries. The authors showed that this effect was mediated by Ca^{2+}-activated high-conductance K^+ channel opening and also by endothelial nitric oxide production. Its effect as a hypotensor were also confirmed by da Silva et al. [83], who demonstrated the acute and prolonged role of **9** in lowering blood pressure regulated by nitric oxide-induced K^+ channel opening in smooth muscle cells.

One more compound has also been isolated from Brazilian species and has demonstrated diuretic activity of interest. 2-methoxy4,5-methylenedioxy-*trans*-cinnamoyl-pyrrolidine [10], isolated from *Piper glabratum* Kunth, was also shown to be effective in inducing diuresis (30 mg/kg) associated with urinary HCO_3^- elimination, with no interference in the other parameters [84].

Despite the large number of studies with extracts and fractions, it can be seen that there have been few studies with isolated compounds that focus on diuresis and renal protection, and most of those that do exist involve animal models. Thus, a wide range of research remains to be carried out on chemical compounds found in previously studied plants, or common compounds of interest that have already shown action and effectiveness in the cardiovascular system, but their renal effects have not yet been evaluated.

Future Prospects

Despite the popular appeal of well-known plants in all regions of Brazil, scientific studies to properly validate these attributed effects are still scarce or preliminary. In this section, we list the main native and/or well cultivated medicinal plants in Brazil that have not yet been the subject of either preclinical or clinical studies on their indication as diuretics.

The leaves of *Phyllanthus niruri* L., which belongs to the Phyllanthaceae family and is popularly known as “quebra-pedra” in Brazil and “gale of the wind” or “stonebreaker” in English, are used as a diuretic to eliminate kidney stones and for renal colic [85–88]. Its composition includes flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins, and saponins [87–88]. The alkaloids are related to antispasmodic activity, leading to smooth muscle relaxation, mostly evidenced in the urinary tract, which facilitates the elimination of urinary calculi, hence the main application of this species to treat kidney stones [86]. The effects of *P. niruri* on urolithiasis or nephrolithiasis were evidenced in both experimental [89–91] and clinical approaches [92, 93]. Despite all the phytochemical and biological knowledge of this plant, a re-

lated species, *Phyllantus amarus* Schumach., found in the Northeast region of Brazil and with the same popular use, was reported as having diuretic activity in a preclinical study [94]. In fact, the diuretic activity could benefit from the pharmacological effects already described, since the increase in urinary volume, associated with changes in the electrolyte excretion (mainly calcium) could contribute to prophylaxis in the formation of urinary/renal calculi.

Mikania hirsutissima DC., known in folk medicine as "cipó-cabeludo" or "hair clematis" in English, is another representative plant of this list. It has been popularly used as a diuretic and in the treatment of kidney stones, cystitis, nephritis, and hyperuricemia [95–97]. Despite being widely used in traditional Brazilian medicine, studies with this species are scarce. The only studies that exist have focused on its possible anti-inflammatory activity [98] and phytochemical characteristics [99].

Another well-known species is "sabugueiro", scientific name *Sambucus australis* Cham. & Schltdl., which has been popularly used for its antiseptic and anti-inflammatory properties in the treatment of kidney stones and as a diuretic [100]. Although some of its properties have already been proven, especially those related to the anti-inflammatory, antioxidant, and antimicrobial effects [101–103], there have been no studies on its possible renal actions. All parts of this plant have been used in natural medicine in various parts of the world for centuries, but nowadays the dried flowers tend to be mainly used. However, the leaves are reported to contain a toxic cyanogenic glycoside and should not be used orally. In fact, the leaves are considered insecticides and are occasionally used in the preparation of homemade insecticides [8].

A plant species with vigorous growth that is native to the riparian forests of the Southeast region of Brazil, *Rubus brasiliensis* Mart., commonly known as "amoreira-do-mato", is an important representative when it comes to diuretic properties. Its fruits are edible and are appreciated by the population of the rural region, while the other parts of the plant are used in traditional medicine. The leaves and roots are used to prepare infusions that serve as a diuretic medication [104]. While the scientific validation of its possible diuretic effect remains unknown, some studies suggest that preparations obtained from *R. brasiliensis* have actions on the central nervous system [105, 106].

Alternanthera brasiliana (L.) O. Kuntze, popularly known in Brazil as "carrapichinho", is a native plant in Brazil, and the infusion of its leaves is considered diuretic [11]. However, only studies focusing on its healing [107], antioxidant [108], anxiolytic, and anticonvulsant [109] properties have been conducted so far. Similarly, the dry peels and leaves of *Schinus mole* L., popularly known in Brazil as "aroeira" and native to southern Brazil, are used as a diuretic [96]. Among the biological properties already described, it has potential antifungal and antibacterial [110], analgesic, anti-inflammatory, and sedative effects [111].

Another well-known and widely-studied plant is *Pistia stratiotes* L., popularly known in Brazil as "erva-de-santa-luzia" and in English as "water lettuce" or "tropical duckweed", its leaves are used in the preparation of teas for diuretic purposes [11], although there are no scientific data on this specific use. Similarly, *Tabebuia avellanedae* Lor. Ex Grisep., native to America and occurring throughout Brazil, is known in folk medicine as "ipê-comum". The ethnobotanical literature mentions the use of its peels for the preparation of teas with anti-infectious and diuretic properties [112]. However, despite several scientific studies available in the literature, there are still no reports on the validation of its use as a diuretic.

The species *Tagetes erecta* L. is popularly known in Brazil as "cravo-de-defunto". In English-speaking countries, it is called "marigold" and "African-marigold". In Mexico, Central America, and other countries in South America, it is known as "amarillo" and "flor-de-muerto". Its flowers are used in folk medicine as antihypertensive and diuretic [113, 114]. *Tagetes minuta* L. is another species in the genus *Tagetes*, popularly known as "cravo-de-defunto", with indication in folk medicine for diuretic purposes [10]. Both species present reports in the literature of both phytochemical and pharmacological potential. However, no study has proven their popularly attributed diuretic effects.

For centuries, the Guarani Indians of Paraguay and Brazil have used *Stevia rebaudiana* (Bertoni) Bertoni leaves, popularly known as "estévia", as a sweetener and for medicinal purposes as a hypotensive and diuretic [100]. The scientific literature on this plant is vast. However, in terms of its diuretic potential, only 1 study suggests the action of this species, having tested the plant extract through an intravenous infusion in rats [115]. Notably, the abovementioned study was only a very preliminary study, and its form of administration was different from the way the plant is popularly used. Therefore, the effects of this species remain to be investigated using appropriate methodology.

Another medicinal plant with edible fruits is the species *Ananas comosus* (L.) Merr., known as "abacaxi" or "pineapple". It is widely cultivated throughout Brazil, mainly for consumption of the fruit, and is used as diuretic [11]. Several works in the literature have reported on the medicinal properties of *A. comosus*. However, only 1 study points to the validation of its possible diuretic action. The data from this study reveal that root extracts of *A. comosus*, at a dose of 10 mg/kg, significantly increased urine output and electrolyte excretion when given orally to rats [116]. But that study is limited to an initial screening of biological activity, and the effects of this species have yet to be studied under other conditions (i.e., at other doses, using other parts of the plant, and with other experimental models), in addition to evaluating the mechanisms of action of preparations at the cellular and molecular levels.

Conclusions

The rich Brazilian biodiversity demonstrates an immense variety of plants with therapeutic potential, including diuretic effects and associated pathologies, the focus of this review. Although many medicinal plants are used in traditional Brazilian medicine for their possible diuretic action, few clinical studies have been conducted to investigate this action, and it needs to be more explored. However, although purely descriptive and lacking in in-depth analysis of the mechanism of diuretic action, there have been many experiments that confirm, at least in part, the beneficial potential of many plants, which are generally selected for study based on their popular use in folk medicine. In this context, several plants can be indicated for more detailed study, with a view to obtain scientific subsidies for a new and effective diuretic

medicine in the future. These include *B. forficata, L. dasytricha*, and *T. majus*. On the other hand, there are several examples of plants for which diuretic potential has been discovered but which are not used in popular medicine for this purpose. These include *G. achachairu, M. bimucronata*, and *M. eugeniopsoides*. Other species have reputed medicinal properties but lack experimental assays to demonstrate their pharmacological effects (e.g., *M. hirsutissima, P. niruri,* and *T. minuta*). Several active principles are indicated as responsible for the diuretic effects of the plants studied, with emphasis on phenolic compounds as flavonoids, phenolic acids, and xanthones. Taken together, the results should encourage more detailed preclinical, clinical, and phytochemical investigations on Brazilian plants in the future, with the aim of discovering new and effective medications to treat diuresis and/or associated ailments.

Contributors' Statement

Design of the study: P. de Souza, V. Cechinel-Filho; data collection: P. de Souza, L. N. B. Mariano, C. C. Cechinel-Zanchett, V. Cechinel-Filho; drafting the manuscript: P. de Souza, L. N. B. Mariano, C. C. Cechinel-Zanchett, V. Cechinel-Filho; critical revision of the manuscript: P. de Souza, V. Cechinel-Filho.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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