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Revisión | Review

Passiflora alata Curtis: a Brazilian medicinal plant

[*Passiflora alata* Curtis: una planta medicinal Brasileña]

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Abstract
This review describes botanical, chemical, pharmacological and phytotechnological properties of *Passiflora alata* Curtis, with emphasis on analytical methods. Native to Brazil, *P. alata* is featured in several pharmaceutical preparations registered by the regulatory agency ANVISA. In four of the five editions of the Brazilian Pharmacopoeia, *P. alata* leaves have been included under the designation of "maracujá" or "maracujá doce" (sweet passion fruit). This species is cited as *Passiflora alata* Curtis and was originally published in 1788 in the Botanical Magazine. In the last decade, phytochemical and pharmacological studies of Brazilian researchers related to this plant have increased. Despite several studies, the substances responsible for the anxiolytic, sedative, antioxidative and antiulcer activities attributed to *passifloras* remain unknown. Analytical methods for the quantification of markers are being developed in order to improve quality control analysis and to better understand the relationship between chemical markers and their pharmacological effects. Those methods include spectrophotometry, high performance thin-layer chromatography (HPTLC) and high performance liquid chromatography (HPLC). There is also great interest in the technological processes involved in the production of dry extracts of this native medicinal plant with the primary goal of assuring the quality of phytopharmaceutical products.

Keywords: Maracujá, *Passiflora alata* Curtis, Review, Pharmacological Activity, Marker Substance, Medicinal Plant.

Resumen
En esta revisión se describen las caracteristicas botánicas, químicas, farmacológicas y fitotecnologicas de *Passiflora alata* Curtis, con enfasis en los métodos analíticos. Originaria de Brasil, varias preparaciones farmacéuticas de *P. alata* son registradas por el organismo regulador ANVISA. En tres de las cinco ediciones de la Farmacopea Brasileña, las hojas de *P. alata* se han incluido bajo la denominación de "maracuyá" (fruta de la pasión). Esta espécie deve ser citada como *Passiflora alata* Curtis, publicada originalmente en 1788 en "Botanical Magazine". En la última década, los estudios fitoquímicos y farmacológicos de investigadores brasileños relacionados con esta planta han aumentado substancialmente. A pesar de varios estudios, las sustancias responsables de las actividades ansiolítica, sedante, antioxidante y antiulcerosa atribuidas a la passiflora continuan siendo desconocidos. Los métodos analíticos para la cuantificación de los marcadores están siendo desarrollados con el fin de mejorar el análisis de control de calidad y para comprender mejor la relación entre marcadores químicos y sus efectos farmacológicos. Estos métodos incluyen espectrometría de alto rendimiento, cromatografía en capa fina (HPTLC) y la cromatografía líquida de alta resolución (HPLC). También existe un gran interés en los procesos tecnológicos envueltos en la producción de extractos secos con el objetivo principal de asegurar la calidad de los productos fitosanitarios.

Palabras Clave: Maracujá, *Passiflora alata* Curtis, Revisión, Actividad Farmacologica, Substancia Marcadora, Planta Medicinal

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1. INTRODUCTION

The use of natural products, especially those derived from plants, is one of the oldest forms of medical treatment for sickness and injury. Scientific interest in herbal drugs has increased considerably during the last ten years, and efforts have been made to understand the basis of the medicinal properties of plants (Newman *et al.*, 2003; Mahmmoud, 2007).

The Passifloraceae family is distinguished from other plants used in Brazilian folk medicine due to its extensive use in the treatment of a wide variety of diseases. The *Passiflora* genus comprises about 400 species and is the most important genus of this family. Passifloraceae is represented by approxima-tely 23 genera and 600 species distributed mainly in tropical and subtropical regions, many of them in Brazil. There are four genera with about 80 species and a wide geographical distribution that are native to Brazil. Most of these species related to the *Passiflora*, and products derived from these plants are internationally recognized as herbal medicines (Carlini, 2003).

The most well-known species of this family is *Passiflora incarnata* L., found in Europe and North America. It is included in the pharmacopoeia of most countries, as well as the British Herbal (British Herbal Pharmacopeia, 1996), French (Pharmacopée Francaise, 1992) and European (European Pharmacopeia, 2007) pharmacopoeias. In Brazil, species of the *Passiflora* are known as "maracujá" (passion fruit). *P. alata* and *P. edulis* are the only passion fruit species currently cultivated on a commercial scale. They are mainly produced in Sao Paulo State and their fruit is consumed *in natura* or in juices and ice creams (Souza and Meletti, 1997).

P. alata, originally published in 1788 in the Botanical Magazine (Curtis, 1770, Bernacci *et al*., 2003; Trópicos, 2010), is native to Brazil and is used in several pharmaceutical preparations that are registered by the regulatory agency ANVISA "Agência Nacional de Vigilância Sanitária" (Nascimento *et al*., 2005; Carvalho *et al*., 2008; Brasil, 2011). In three of the five editions of the Brazilian Pharmacopeia (Silva, 1929; Farmacopeia dos Estados Unidos do Brasil, 1959; Farmacopéia Brasileira, 1977; Brandão *et al*., 2009) its leaves have been designated as "maracujá" and the fifth edition it is cited as "maracujá doce" (Brasil, 2010).

In the last decade, the number of phytochemical and pharmacological studies related to this vegetal species has increased. One of the pioneering phytochemical studies with *P. alata* was carried out by Ulubelen and collaborators (1982), who identified the flavonoids C-glycosides 2"-xilosylvitexin, vitexin, isovitexin and orientin. More recently, Brazilian researchers have investigated the phytochemistry and pharmacology of *P. alata* leaves (Pereira, *et al.* 2000, 2005; Petry *et al.* 2001; Amaral *et al.*, 2001; Reginatto *et al.*, 2001, 2004, 2006; De Paris *et al.*, 2001; Birk *et al.*, 2005; Rudnicki *et al.*, 2007a, b; Vargas *et al.*, 2007, Barbosa *et al.*, 2008). A study sought to examine herb use among Hispanic females with Type II diabetes enrolled in two Community Health Centers in the Southwest USA reported the use of *P alata* (Johnson *et al*., 2006).

Despite several studies, the active substances responsible for the anxiolytic and sedative effects attributed to passifloras have not been defined. In 2004, two works using analytical methods to quantify substances in passifloras were reported. The first of these studies used HPTLC and HPLC methods to quantify flavonoids (Pereira *et al.*, 2004). In the second, Reginatto *et al*., 2004 presented the quantification of a saponin extracted from leaves of *P. alata* (quadranguloside) by HPLC-UV. Early in the following year, Müller *et al*., 2005 used an HPLC-UV method to detect flavonoids present in *P. alata* medicinal extracts and leaves.

Only two Brazilian studies, Runha *et al.*, 2001 and Oliveira *et al.*, 2006, have examined the technological processes involved in the production of dry extracts of this native medicinal plant.

The original review of *P. edulis* and *P. alata* was published almost ten years ago by Pereira and Vilegas (2000). In 2004, Dhawan and collaborators described the prominent species of the genus *Passiflora* and briefly discussed the species *P. alata*. In another review, the composition, efficacy and safety of *P. edulis* was reported (Zibadi and Watson, 2004). More recently, a review was published on morphology, phytochemistry and pharmacological aspects from *Passiflora incarnata* Linn (Patel *et al.*, 2009). A bibliographic review of passion fruit (*P. edulis* and *P. alata*) as a functional food, with emphasis on the fruit was reported by Zeraik *et al*. (2010). Considering the number of recently published papers, it is important to provide a current and systematic review of the scientific literature focused on *P. alata* leaves (Oliveira *et al*., 2007).

2. PHARMACOBOTANICAL DESCRIPTION

"Maracujá doce' complies with the requirements of the Brazilian Pharmacopoeia (Brasil, 2010) and consists of the dried leaves of *Passiflora alata* Curtis. This plant is one of several Brazilian species of

Passifloraceae with edible fruits. Its ellipsoid fruit turns orange when ripe, has aromatic scent and sweet taste. Its leaves are bitter and the odour is characteristic.

This Pharmacopoeia provides the diagnostic value of individual characters at the species level. Its leaves are simple, petiolate, glabrous, subcoriaceous, broadly ovate to oblong, 7-20 cm long and 4-15 cm wide. The base is rounded to slightly reentrant, apex acuminate and margin entire, smooth or somewhat undulate. The adaxial surface is brownish-green and the abaxial surface paler. The venation pinnate is more obvious on abaxial surface. The petiole 2-7 cm long is deeply channeled, having one or usually two pairs of extrafloral nectaries. Tendrils occur in the axils of the leaves.

The preliminary anatomical study of its leaves shows common characters of *Passiflora*: hypostomatic leaves; dorsiventral mesophyll, collateral bundles and clusters of calcium oxalate. The epidermis is uniseriate. In frontal view it has polygonal cells with straight or slightly sinuous anticlinal walls, smooth cuticle and usually anomocytic stomata. The mesophyll is composed of one to three layers of palisade parenchyma and several layers of spongy parenchyma. Clusters of calcium oxalate occur in parenchyma and in the region of the ribs. In the transverse section through midrib, the adaxial surface presents convexity and the abaxial surface is obtusely angled. Subjacent to both surfaces, several layers of collenchyma are observed. The midvein is a broad arc and may be bounded adaxially and abaxially by fiber layers. The petiole is convex at abaxial and depressed at adaxial surface with two lateral projections. Collenchyma occurs at least in the adaxial and abaxial subepidermal positions. The vascular system in arc is surrounded by a sclerenchymatous sheat. Clusters of calcium oxalate of varying sizes may be found in mesophyll and midrib ground tissue.

3. PHYTO-CONSTITUENTS

The chemical composition of *P. alata* presents some divergence. A study to determine the chemical composition of medicinal plants made use of high-speed extraction and HPLC for fingerprinting. The C-flavonoid glycosides schaftoside, isoschaftoside, isoorientin, orientin, isovitexin and vitexin were chosen as analytical standards and their overall prevalence in all samples was determined. In *P. alata*, the marker flavonoids could not be detected in percent concentrations. Only traces of vitexin were observed in the *P. alata.* The other tested flavonoids, including orientin and swertisin (*P. incarnata* markers), hyperoside, rutin, hesperidin and clorogenic acid were absent (Müller *et al*., 2005). In another study in which compounds were analysed by TLC, the vitexin band was not identified; a blue band indicated the presence of phenolic carboxylic acids such as caffeic acid (Pereira *et al*., 2004). Flavonoids are the main constituents, and are ussualy used as biomarkers (Petry *et al*., 1998). The main constituents are shown in Table I; flavonoids and saponins are reported to be the major compounds found in *P alata.*

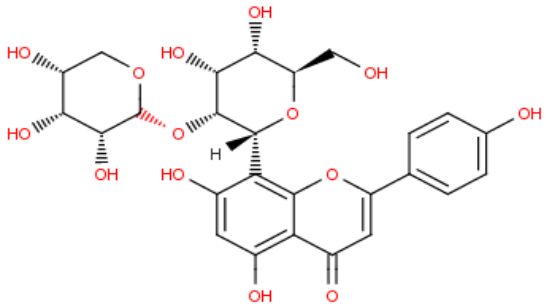
Table I. The main constituents present in *Passiflora alata*

Phyto-constituents	References
Flavonoids	
2”-xylosylvitexin (**1**)	Ulubelen, 1982
Vitexin (**2**)	Ulubelen, 1982, Pereira et al., 2005
Isovitexin (**3**)	Ulubelen, 1982, Müller *et al.*, 2005, Pereira et al., 2005
Orientin (**4**)	Ulubelen, 1982
Rutin (**5**)	Freitas, 1985; Oga *et al.*,1984; Moraes *et al.*, 1997
Vitexin-2’’-O-rhamnoside (**6**)	Pereira *et al*., 2004
Steroid glycoside	
3-O-β-D-glucopyranosyl-stigmasterol (**7**)	Reginatto *et al.*, 2001
Triterpene saponins	
3-O-β-D-glucopyranosyl-oleanolic acid (**8**)	Reginatto *et al.*, 2001

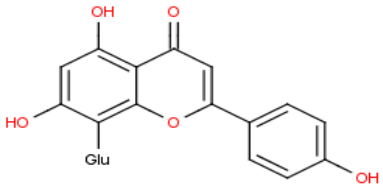
3-O-β-D-glucopyranosyl-(1→3)-β-D-glucopyranosyl-oleanolic acid (**9**)	Reginatto *et al.*, 2001
3-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranosyl-oleanolic acid (**10**)	Reginatto *et al.*, 2001
9,19-cyclolanost-24*Z*-en-3β,21,26-trihydroxy-3,26-di-O-gentiobiose (quadranguloside). (**11**)	Reginatto *et al.*, 2001
Alkaloids	
Harman (**12**)	Freitas, 1985; Machado *et al*., 2010.

Figure 1
Chemical structure of the main constituents present in *Passiflora alata* Curtis

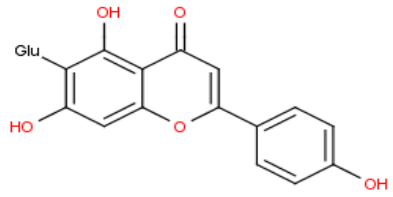
2”-xylosylvitexin (**1**)



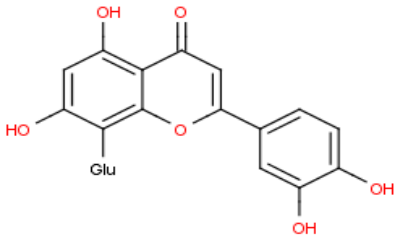
Vitexin (**2**)



Isovitexin (**3**)

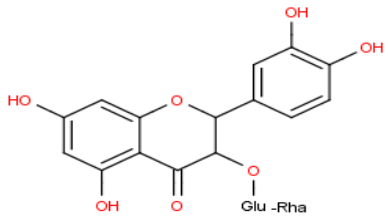


Orientin (**4**)



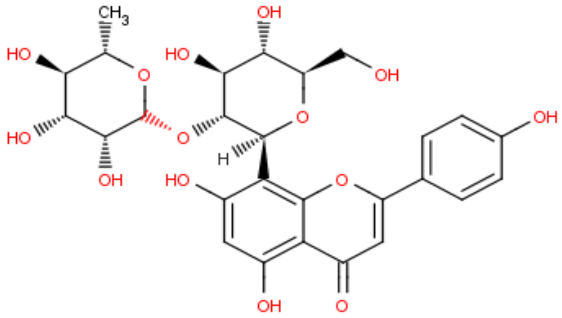
Glu = ß-D-glucopyranosyl

Rutin (**5**)

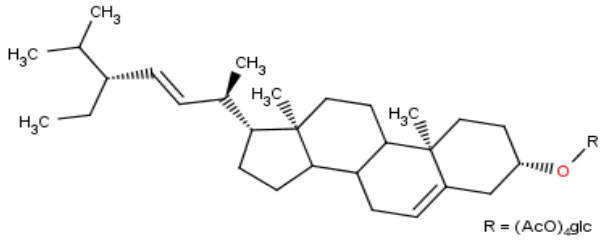


Rha = α-L-rhamnopiranosyl
Glu-Rha = glucose-rhamnose

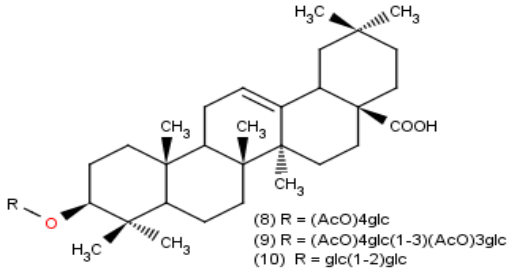
Vitexin-2''-O-rhamnoside (**6**)



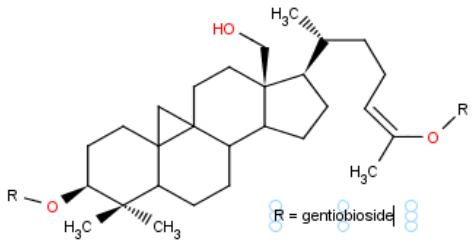
3-O-β-D-glucopyranosyl-stigmasterol (**7**)



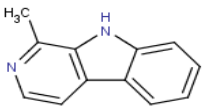
3-O-β-D-glucopyranosyl-oleanolic acid (**8**)
3-O-β-D-glucopyranosyl-(1→3)- β-D-glucopyranosyl-oleanolic acid (**9**)
3-O-β-D- glucopyranosyl-(1→2)- β-D-glucopyranosyl-oleanolic acid (**10**)



9,19-cyclolanost-24*Z*-en-3β,21,26-trihydroxy-3,26-di-O-gentiobiose (**11**)



Harmane (**12**)



4. ANALYTICAL METHODS

The use of thin-layer chromatography (TLC) for the purpose of identification of chemical constituents is described in Table II. Analytical reports using spectrophotometry to quantify compounds are displayed in Table III. Table IV summarizes the results obtained from high performance liquid chromatography (HPLC) methods.

Table II. Analysis of *Passiflora alata* by TLC

Author/year	Reference Substances	Method specifications		
		Plates	**Mobile phase**	**Visualization**
Petry *et al.*, 2001	**Flavonoids** Vitexin Isovitexin Orientin Isoorientin	Aluminum GF_{254}	**Flavonoids** Ethyl acetate:formic acid:acetic acid:water	Methanolic solution diphenilboriloxiethylamine (0.5%) and PEG200 (30% p/v). 105°C.

	Chrysin		(80:1:8:10) v/v.	Short and long-wave UV light.
	Triterpenoids		**Triterpenoids**	
Reginatto *et al.*, 2001	Steroid glycoside and four triterpene saponins (quadranguloside).	Aluminium GF_{254}	$CHCl_3$:EtOH:AcOH (60:40:6) v/v.	Anisaldehyde H_2SO_4. 100°C
De Paris *et al.*, 2002	**Flavonoids** Vitexin Isovitexin Orientin Isoorientin Chrysin	Petry *et al.* 2001.	Petry *et al.* 2001.	Petry *et al.* 2001.
Birk *et al.*, 2005	Vitexin 3-O-β-D-glucopyranosyl(1→3)-β-D glucopyranosyl-oleanolic acid Quadranguloside	Aluminium GF_{254}	**Flavonoids** AcOEt: acetone:AcOH:H_2O (60:20:10:10, v/v) **Saponins:** CHCl3:EtOH:AcOH (60:40:5, v/v)	**Flavonoids** Methanolic solution diphenilboriloxiethylamine (0.5%) and PEG400 (5% p/v) Anisaldehyde H_2SO_4. 100°C **Saponins:** Anisaldehyde H_2SO_4. 100°C UV366.
Reginatto *et al.*, 2006	Present only two major spots with chromatographic profile of flavonoids (one yellow and another one orange)	Birk *et al.*, 2005	Birk *et al.*, 2005	Birk *et al.*, 2005

According to the authors, the flavonoid composition of a *P. alata* extract was simpler than an extract of *P. edulis*. In the *P. alata* extract, three spots were detected by TLC that had characteristic flavonoid color. Saponins were observed exclusively in *P. alata* (De Paris *et al.*, 2001). The *P. alata* extract presented two spots with characteristic flavonoid color; however, their R_F values were not the same as any flavonoid used as a reference substance (Birk *et al.*, 2005). In *P. alata*, only two major spots were observed; these major compounds showed chromatographic profiles of flavonoids (one yellow and another one orange) and saponins. In *P. edulis*, the C-glycosides vitexin and orientin were identified (Reginatto *et al.*, 2006).

Table III
Analysis of *Passiflora alata* by Spectrophotometry

Author/ Year	**Reference Substances Tested**	**Method specifications**		
		Evaluation	**References**	**Results**
Petry *et al.*, 2001	**Flavonoids** Apigenin	UV absorption of the $AlCl_3$–flavonoid complex. Detection 392 nm. HP 5820 spectrophotometer.	Schmidt and González Ortega (1993) and Petry *et a.l* (1999).	Content of flavonoids of *P.edulis* twice *P. alata* (4.60 vs. 2.90 p/p).
De Paris *et al.*, 2002	**Flavonoids** Apigenin	UV absorption of the $AlCl_3$-flavonoid complex. HP 5820 spectrophotometer.	Petry *et al.*, 2001.	Content of flavonoids of *P.edulis*: (4.04%) *P. alata* (1.90%). λ_{max} at 278, 300, 400 nm.
Müller *et al.*,2005	**Flavonoids** **Helvetica**	UV–vis double array spectrophotometer	*Passiflora incarnata* monograph	**Helvetica Pharm.:** within the limits predetermined

	Pharm.: Hyperoside **British Pharm.:** Vitexin	SHIMADZU UV-601.	(Pharmacopoeia Helvetica and British Pharmacopoeias)	for *P. incarnata* (0.3%). **British Pharm.:** Under the lower limit, with total flavonoid value of 0.55g%
Reginatto *et al.*2006	According to Petry, 2001	According to Petry *et al*, 2001	Petry *et al.*, 2001	Total flavonoid content; 2.9 % *P. alata* 4.0 % *P. edulis*.
Barbosa *et al.*, 2008	Apigenin	Ultraviolet Absorption of the $AlCl_3$-flavonoid complex.		λ_{max}: 398 nm. Flavonoids content: 2.1% for *P. alata* and 3.9% for *P. edulis.*
Chabariberi *et al*., 2008	Rutin	Theoretical λmáx = 394 nm (**French. Pharm**.) and 401 nm (**European Pharm**.).	*Passiflora incarnata* (Modification of the procedures from French and European Pharmacopoeias)	Practical λmáx = 427 nm (**French. Pharm**.) and 430 nm (**European Pharm**.).

An approach comprising accelerated solvent extraction followed by quantitative HPLC analysis was adopted in fingerprinting 115 samples of different species of *Passiflora*. In *P. alata* was detected a common unidentified peak eluting at 40.0 min. Such a peak had characteristic UV absorbance maxima at 267 and 337 nm suggesting a closely related analog of the chosen markers studied: schaftoside/isoschaftoside, isoorientin, orientin, isovitexin and vitexin (Abourashed *et al*., 2002).

Pesticide residue is generally unacceptable in medicinal plants and the literature shows analytical methods to determine it. Da Silva and collaborators (2007) achieved promising results using a simultaneous optimization strategy based on neuro-genetic approach applied to a HS-SPME-GC-ECD (Headspace Solid Phase Microextraction coupled to Gas Chromatography with Electron Capture Detection) method for simultaneous determination of the pesticides chlorotalonil, methyl parathion, malathion, α-endosulfan and β-endosulfan in herbal infusions of *P. alata*.

5. PHARMACOLOGY AND TOXICITY

The first report describing the pharmacological activity of *P. alata* came from Oga and collaborators in Brazil in 1984. They found that an extract made from *P. alata* leaves increased the induction of sleep by pentobarbital in rats. It also increased the latency time caused by the pentylenetetrazole-induced seizures and decreased spontaneous motor activity when administered by the intraperitoneal route at 75 and 150 mg/kg. They found an LD_{50} value of 456 mg/kg for the extract (Oga *et al*., 1984).

Another study compared the pharmacological activity of hydroethanol extracts of *P. alata* and *P. edulis* leaves. The anxiolytic activity was evaluated using the elevated plus-maze test, and the chemical composition of hydroethanol extracts of *P. alata* and *P. edulis* leaves was determined. Diazepam (1 mg/kg) was used as a standard anxiolytic drug. All groups tested were compared with saline. The extracts presented anxiolytic activity in dosages around 50, 100 and 150 mg/kg. With respect to the phytochemical analysis, the hydroethanol extracts of *P. edulis* leaves presented almost twice the flavonoid content than *P. alata* (Petry *et al*., 2001).

In 2001, De Paris carried out a similar study using aqueous extracts instead of hydroethanol extracts. Once again, the phytochemical results showed that aqueous extracts of *P. edulis* leaves presented twice the flavonoid content of *P. alata*. By comparing these results with those of the previous study, the authors determined that the solvent (ethanol 40 °GL or water) did not qualitatively change the chemical composition with respect to flavonoids and saponins and, moreover, aqueous and hydroethanol extracts had identical anxiolytic effects. The intraperitoneal administration of *P. alata* at doses of 100 and 150 mg/kg and of *P. edulis* at doses of 50, 100 and 150 mg/kg showed anxiolytic effects according to the elevated plus-maze model (De Paris *et al.*, 2001).

In 2006, Reginatto *et al.* compared the potential anxiolytic activities of two *Passiflora* spray-dried powders obtained from *P. alata* and *P. edulis* by oral administration. The activity profiles of the extracts were the same as those previously reported for freeze-dried extracts of *P. alata* and *P. edulis* administered intraperitoneally (Petry *et al.*, 2001; De

Paris *et al.*, 2001). Similar to diazepam, animals treated with spray-dried extracts of *P. alata* (800 mg/kg) and *P. edulis* (400 and 800 mg/kg) showed an anxiolytic effect demonstrated by a significant increase in the number of entries and permanency in open arms (p <0.05), as well as a decrease in the time spent in closed arms (p <0.05).

Table IV
Analysis of *Passiflora alata* by High Performance Liquid Chromatography (HPLC)

Author/year	Scope	Column	Detection	Elution	Results
De Paris *et al.*, 2002	Qualitative analysis of flavonoids: Vitexin, Isovitexin Orientin, Isoorientin Chrysin.	NovaPack RPC18 (3.9 x 150 mm i.d., 4 μm)	Ultraviolet detector (Waters, model 486), integrator (Waters 746). Peak identification photodiode-array detector (Waters PDA 996), performed at 340 nm.	Acetonitrile: Phosphoric acid 0.05% (20:80, m/m), flow rate of 0.8 ml/min. at 21± 2 °C	*P. alata* 5 substances with retention time (R_T) different from the reference substances.
Müller *et al.*, 2005	Qualitative analysis of flavonoids: Orientin, Swertisin Vitexin, Hiperoside Rutin, Hesperidin and Clorogenic acid.	Luna RPC18 (5um) Phenomenex	Photodiode array detector.	Isocratic elution (CAN–H_2O–HOAc 18:82:0.5) with a 1 mL/min flow. Isovitexin was determined by external standard method, gradient elution mode*	*P. alata*: traces of vitexin and isovitexin. Not found: orientin, swertisin, rutin.
Pereira *et al.*, 2004, 2005	Quantitative analysis of total flavonoids: Rutin, vitexin, isoorientin and orientin. Validation of analytical procedures.	Supelco RP18 column (250 x 4.0 mm i.d.; 5 μm)	Photodiode array detector at 337 nm for detection.	solvent A [2.0% formic acid (99%;) in water] and solvent B [HPLC grade acetonitrile]** flow-rate was 0.8 mL/min. 35°C.	Total flavonoid content showed no significant statistical difference.
Reginatto *et al.*, 2004, 2006	Quantification of saponin quadranguloside. Validation of analytical procedures.	Waters Nova-Pack Phenyl column (150 x 3.9 mm i.d.; 4 μm)	Detection was at 205 nm and 0.1 AUFS	Acetonitrile : 0.1% aqueous phosphoric acid (29:71, v/v), flow rate of 1.0 mL/min. Room temperature (22±2°C)	Content of quadranguloside: 22.2%(w/w), corresponding to 0.8% (w/w) in relation to the dried leaf samples.

*Isovitexin was determined in plant material according to an external standard that was diluted (MeOH 50%) to 4.0, 8.0, 12.0, 16.0 and 20.0 μg/mL. Standard concentrations were produced in triplicate. A gradient elution mode with a 1 mL/min flow was employed: 1–20 min 10% solvent B (MeOH) and C (ACN) in A (H_2O–HOAc, 100:0.5, pH 2.88), 20–30 min 15% B and C in A, 30–35 min 20% B and C in A. (Müller *et al.*, 2005)

** The separation was performed using gradient elution: 0–10 min 15% B in A, 10–40 min 15–30% B in A and 40–50 min 30–15% B in A.

P. alata extract was administrated orally in rats at dose of 1000 mg/kg and it was observed an increase in high-density lipoprotein level (HDL-cholesterol) (Doyama *et al.*, 2005). More recently, Rudnicki *et al.*, (2007a, 2007b) studied the antioxidant and hepatoprotective activities of *P. alata*. In the first trial (Rudnicki, 2007a), the antioxidant activity was determined by *in vivo* (Total Reactive Antioxidant Potential) and *ex vivo* (in rat liver slices) assays. Their results showed a high level of activity (DE_{50} = 171 mcg/mg), and they related the activity to the total phenolic compounds. In a second trial (Rudnicki, 2007b), they showed a hepatoprotective effect of *P.*

alata on carbon tetrachloride induced oxidative damage in rats. The extract reduced the levels of markers of liver failure (ALT, AST) and histopathological changes in the samples. Other study showed significant antioxidante activity of *P. alata* and *P. edulis* on stimulated neutrophils (Zeraik *et al*., 2011).

In another study, the antiulcer activity of *P. alata* was evaluated, doses of 100, 200 e 400mg/kg of extracts were tested in the same conditions with HCl 150 mmol/L versus lanoprazole. *P. alata* showed 100% of protection in total lesion area (TLA) at the three concentrations studied, while lansoprazole showed 75% of protection (Wasicky, 2007).

Studies evaluating the pharmacological activities of *P. alata* showed interesting results, demonstrating anticonvulsant and anxiolytic activities (Romanini et al., 2006; Provensi *et al*., 2008; Quintans Junior *et al*., 2008; Sousa *et al*., 2008). Some studies have been made in order to evaluate toxicity of *Passiflora* extracts (Boeira *et al.*, 2010; Amaral *et al.*, 2001), and all of them showed no toxic effects in dose up to 4800 mg/kg into a single dose, or 300 mg/kg for 14 days. However, the researchers found some DNA damage in dose dependent-manner, after 72 hours of treatment (Boeira *et al*., 2010). Also, Giavina-Bianchi and co-workers, in 1997, presented a case-report of *P. alata*'s and *Rhamnus purshiana*'s induced respiratory allergic disease. They conducted a skin testing and a Western blot and confirmed the sensitization of the patient to these plant extracts, confirming new etiologic agents of IgE-mediates occupational asthma and rhinitis (Giavina-Bianchi *et al*, 1997).

6. PHYTOPHARMACEUTICAL TECHNOLOGY

A study by Runha and collaborators (2001) was conducted in order to develop processes for the production of dry extracts of medicinal Brazilian plants using spouted beds as drying equipment. Passion flowers were used as a model plant. The main conclusion of this work was that an increase in the drying temperature, together with a low feed flow rate of hydro-alcoholic extracts, tended to increase the degradation of flavonoid compounds.

The performance of the spray and spouted-bed dryer and the physicochemical properties of the products resulting from drying the hydro-alcoholic extracts of the three plants *P. alata*, *Bauhinia forficata*, and *Maytenus ilicifolia* were evaluated comparatively by Oliveira *et al.*, 2006.

Recently, Bott *et al*., (2010) carried out a stability study of spray- and spouted bed-dried extracts of *P. alata* under stress storage conditions that suggested the degradation of marker substance (vitexin) and their short shelf lives due to the high hygroscopicy of the extracts.

7. HORTICULTURAL ASPECTS

Sweet passion fruit (*P. alata*) is gaining importance in the *in natura* fruit market due to its differential value. Genetic breeding is crucial to improve crop quality and productivity. In order to evaluate some physical characteristics and the nutrient distribution in sweet passion fruit a study was carried out by Vasconcellos *et al*. (2001). The pollination biology of *P. alata* was studied in south-eastern Brazil, specifically the importance of chemical features of floral nectar, pigments and odours. Bees are the pollinators required by *P. alata* to produce fruits (Varassin *et al*., 2001). Fourteen horticultural characteristics of five sweet passion fruit (*P. alata*) populations were evaluated, and a considerably high variability among plants and low among populations was observed for these characters by Martins *et al*. (2003). The geographical distribution, ecological characteristics, flowering and fruiting times, and pollinating agents of *P. alata* were considered and related to molecular genetic data gathered simultaneously by Koehler-Santos *et al*., (2006a, 2006b). The best treatment to enhance the growth of sweet passion fruit (*P. alata*) seedlings was evaluated by various authors (Veras *et al*., 2000; Leonel and Pedroso, 2005, Ferreira *et al*., 2005; Freitas *et al.*, 2006; Freitas *et al*., 2008; Roncatto *et al*, 2008). Damatto and collaborators (2005) evaluated the influence of organic fertilizers for production of *P. alata* and verified better quality and larger production of fruits. Another study performed by Lima *et al*. (2006) verifed the germination and speed of emergence index of passion fruit species to obtain plants suitable for grafting. The genetic variability of 17 sweet passion fruit accesses, using RAPD molecular markers was studied by Bellon *et al*. (2009). The environmental conditions influence on storage of sweet passion-fruit (*P. alata*) seeds was studied, after twelve months, seeds with humidity close to 10% and conditioned in plastic bags showed better conservation, when maintained at 10ºC (Osipi and Nakagawa, 2005).

8. LEGAL ISSUES

The use of *P. alata* was officially recognized in the first edition of Brazilian Pharmacopoeia (Silva, 1929) where it was described as "Maracujá": *Passiflora alata* Aiton. The treatments described are in the form of fluid extracts and tinctures of its leaves. In the second edition (Farm. Bras. II, 1959), the fluid extract was deleted. In the third edition (FBRAS., 1977) analytical methods for the quantification of flavonoids and alkaloids in the plant were included. More recently, *P. alata* Curtis was cited in the fifth edition (Brasil, 2010).

The Resolution RE Nº 89, dated March 16 2004 (Brasil, 2004), resulted in publication of the "List of Simplified Registration Procedures for Herbal Products" on sale as "over the counter" drugs, tinctures and extracts prepared from the leaves of sweet passion fruit. In this case, the referenced plant was *P. incarnata* and not *P. alata* (Brazilian species), and it was indicated as a sedative. This resolution was published in the Official Executive Gazette on March 18 2004 with the issuing agency: ANVISA - National Agency for Sanitary Surveillance, which is valid for all of Brazil.

In 2005, the "Technical Regulation of Plants for Tea Preparations" was published. It was officially recognized in the Collegiate Board Resolution - RDC Nº 267, dated September 22nd 2005, which includes four species of *Passiflora*, the Maracujá-açú (*P. quadrangularis* L.), the Maracujá-azedo (*P. edulis* f. flavicarpa Degener), Maracujá-doce (*P. alata* Dryand) and Maracujá-roxo (P. *edulis* Sims.) (Brasil, 2005).

Resolution 89 was then repealed by the normative instruction n°5, dated December 11th 2008. The "List of Herbal Medicines Simplified Registration" was approved. *P. incarnata* was still featured, but was indicated as a mild anxiolytic and the entry was modified to include only vitexin as an expressed flavonoid.

In February 2009, a list of 71 medicinal plants was proposed. This list was named RENISUS – the National List of Medicinal Plants of Interest for the Public Health System. The passion fruit monograph listed *Passiflora* spp., and it included *P. alata*, *P. edulis* and *P. incarnata* (Brasil, 2009). In 2010, the monographs of *P. edulis* and *P. alata* were approved in public consult for inclusion on fifth Brazilian Pharmacopoeia (Brasil, 2010).

10. FINAL CONSIDERATIONS

The Brazilian sweet passion fruit *P. alata* is a well-known plant used in South American folk medicine. In Brazil, it is officially recognized as a phytomedicine, and it has been commercialized either alone or in association with other plants (*Crataegus oxycanta, Salix alba, Erythryna mulungu*) for treatment of anxiety disorders. Its pharmacological and phytochemical properties have been studied by many Brazilian groups. *P. alata* is a promising candidate as a phytotherapeutic drug due to its range of activities (antiinflammatory, antioxidant). However, there is controversy regarding its chemical composition and, even if a chemical characterization can be made, there are no proposed biomarkers for this species. Further studies are necessary to determine the phytochemical characteristics of *P. alata* and develop biomarkers assays. Such studies will reveal any correlation between chemical composition and pharmacological activity and allow for distinction between dose-dependent and independent activities.

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