Passiflora alata: A Phytopharmacological Review

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ABSTRACT

Passiflora alata, mainly known as sweet passion fruit, is a flowering plant native to Amazon, usually grown from Peru to Brazil. It is the official Passiflora *species in the Brazilian Pharmacopoeia.* P. alata *is a perennial plant, an evergreen climber native to South America. It is an evergreen vine popularly known in Brazil as 'maracujá-doce' and can grow up to 6 m (20 ft) or more. The main constituents present in Passiflora alata include flavonoids, mainly responsible for their antioxidant property, steroid glycosides, triterpene saponins, and alkaloids. Various analytical methods such as TLC, HPTLC, and spectrophotometry have been utilized to identify chemical compounds. Its leaf extracts have been used in folk medicine in South America because of their sedative and anxiolytic properties. It is also an antioxidant, anti-inflammatory, and gastroprotective agent based on its traditional use for gastric problems. P. alata has been used as a sedative and for anxiolytic purposes. These effects are attributed to specific secondary metabolites such as saponins and C-glycosidic flavonoids. The main saponin constituent, triterpene quadranguloside is considered chiefly responsible for the anxiolytic activity. P. alata acts as a gastroprotective agent based on its traditional use for gastric problems. The antimicrobial activity of acetone, ethyl acetate, and ethanol extract of P. alata (Dried ground plant) material was tested against 27 microorganisms, including 17 strains of bacteria and ten species of Fungi. This review suggests that Passiflora alata is rich in medicinal plants and is already used in folklore and traditional medicine, and much research is needed to develop herbal medicine to address various CNS disorders such as anxiety and convulsions.*

Keywords*: Passiflora alata, review, flavonoids, anxiolytic, antioxidant, antiglycation, antidiabetic.*

INTRODUCTION

Passiflora alata, mainly known as sweet passion fruit, is a flowering plant native to Amazon, usually grown from Peru to Brazil. It is the official *Passiflora* species in the Brazilian Pharmacopoeia and is the second most cultivated species of the genus. Genus *Passiflora* includes more than 400 species. *P. alata* is a perennial plant, an evergreen climber native to South America [1].

It is an evergreen vine popularly known in Brazil as 'maracujá-doce' and can grow up to 6 m (20 ft) or more. It succeeds in lowland tropical to subtropical areas and is mainly cultivated above 5°C. The internode is quadrangular in cross-section. Its ellipsoid fruit turns orange when ripe, and has an aromatic scent and sweet taste. Its leaves are bitter, and the odour is characteristic [2].

The main constituents present in *Passiflora alata* include flavonoids, mainly responsible for its antioxidant property, steroid glycosides, triterpene saponins, and alkaloids. Various analytical methods, such as TLC, HPLC, and spectrophotometry, have been used to identify its chemical compounds [3].

It is broadly cultivated for its edible fruits and is recognized in the local culinary. Its leaf extracts have been used in folk medicine in South America because of their sedative and anxiolytic properties. It is also an antioxidant, anti-inflammatory, and gastroprotective agent based on its traditional use for gastric problems [4].

In Brazil, *P. alata* is a promising candidate as a Phyto therapeutic drug due to its wide range of activities.

Taxonomy

Kingdom:	Plantae
***Clade*:**	Tracheophytes
***Clade*:**	Angiosperms
***Clade*:**	Eudicots
***Clade*:**	Rosids
Order:	Malpighiales
Family:	Passifloraceae
Genus:	*Passiflora*
Species:	*P. alata*

Morphological characteristics

Passiflora alata is an evergreen vine; climbing shrub can grow up to 6m in height or more. The meaning of the specific epithet 'alata' is winged, which refers to its 4-winged stems. It

usually blooms around late summer or early fall, needing full sun exposure and attracting bees, butterflies, and birds. Littoral levees and rainforests are the main habitats of this species. Plants produce tendrils and climb by attaching these to other plants[5].

Seedlings

They contain a hard seed coat and are very slow to sprout. There are various pretreatment methods, but the simplest is to soak the seeds for 24-48 hours in lukewarm water before planting. Seeds can be lightly scarified with sandpaper to permeate the seed coat.

Fruit

Fruits are obovoid, ellipsoid, or pyriform with a pleasant, sweet flavor. It is yellow to bright orange, and can grow up to 8–15 cm (3–6 in) long and 5–10 cm (2–4 in) in diameter. It weighs around 90–300 g (3–11 oz).

Leaves

Leaves are simple, petiolate, glabrous, sub-coriaceous, oval or oblong, 7-20 cm long, and 4-15 cm wide. Sometimes asymmetrically divided and with one tendril in the base. The base is round; the apex is acuminate with an entire margin that is smooth to undulate.

The adaxial surface is brownish-green, and the abaxial surface is paler with pinnate venation. The petiole is 2-7 cm long and usually consists of two pairs of extrafloral nectarines. Tendrils occur in the axils of the leaves.

Midrib shape: Biconvex with slight convexity on the adaxial side and prominent and angular convexity on the abaxial side.

Stems

Stems scramble over the ground or climb into the surrounding vegetation, supporting themselves using coiling tendrils that can grow up to 6m.

Roots

Shallow root system

Flowers

Fragrant granadilla produces large, fragrant flowers and is widely cultivated as an ornamental and for its edible fruit. The fragrant flower is 7–10 cm (3–4 in) wide, with red curved tepals and a prominent fringed corona in bands of purple and white, giving the appearance of stripes [6].

PHYTOCHEMICAL PROFILE

The primary chemical constituents of *P. alata* are flavonoids and saponins. Flavonoids include 2”-xylosylvitexin, Vitexin, Isovitexin, Orientin, Rutin, Vitexin-2’’-O-rhamnoside and Triterpene saponins such as 3-O-β-D-glucopyranosyl-oleanolic acid, 3-O-β-D-

glucopyranosyl-(1→3)-β-D-glucopyranosyl-oleanolic acid,3-O-β-D-glucopyranosyl-(1→2)-β-D- glucopyranosyl-oleanolic acid, 9,19-cyclolanost-24Z-en-3β,21,26- trihydroxy-3,26-di-O-gentiobiose (quadranguloside).

Other constituents present are Alkaloids like Harman and Steroid glycoside such as 3-O-β-D-glucopyranosyl-stigmasterol [7].

PHARMACOLOGICAL PROFILE

Anxiolytic activity

The elevated plus-maze test is a pre-clinical test commonly used for searching for new anxiolytic agents. Male Wistar rats (weighing 250-300 g) were intraperitoneally injected with the aqueous extract of *Passiflora alata*. Diazepam (1 mg/kg) was used as a standard anxiolytic drug. An increase in the time spent in open rodent arms has generally been used as indices for anxiolytic agents. *P. alata* leaf extract at 100 and 150 mg/kg doses showed an anxiolytic effect without memory loss in rats. In contrast, according to the elevated plus-maze model, diazepam disrupted the memory process in rats. On the other hand, it was reported that pure vitexin and isovitexin showed no activity. Isoorientin and orientin possessed very mild anxiolytic effects [8].

P. alata has been used as a sedative and for anxiolytic purposes. These effects are attributed to specific secondary metabolites such as saponins and C-glycosidic flavonoids. The main saponin constituent, triterpene quadranguloside is considered chiefly responsible for the anxiolytic activity [9].

Antioxidant

Fruit extracts are known to contain polyphenols and flavonoids having anti-oxidant properties. They have been used traditionally to treat Alzheimer's disease, cancer, Parkinson's disorder, and liver diseases.

The antioxidant activity of methanol extracts of *Passiflora alata* pulp was investigated using the oxidant activities of the neutrophil and the neutrophil granule enzyme myeloperoxidase (MPO). Both are responsible for playing critical roles in inflammation. The Lucigenin-enhanced chemiluminescence CL method evaluated reactive oxygen species produced by stimulated neutrophils. The activity of purified MPO was measured by SIEFED (Specific Immunological Extraction Followed by Enzymatic Detection), a technique for studying the direct interaction of a compound with the enzyme [10].

Isooreintin was used as standard $4\mu g/mL^{-1}$ and $0.4\mu gmL^{-1.}$

Dose-dependent inhibition of MPO was observed with *P. alata* pulp extracts, reaching approximately 50% of inhibition at the highest concentration tested (1.0 mg mL1 However, the most potent inhibitory effect on the peroxidase activity of MPO was observed with the rind extracts, which showed a 50% inhibitory effect at 0.1 mg mL1. The rind of *P. alata* can be a potential source of molecules with intense antioxidant activity,

These observations suggested that polyphenolic substances in the rind extracts were fixed on MPO (on the enzyme's active site or amino acid of the protein structure) or altered the enzyme structure, leading to MPO inactivation. The study indicated that isoorientin could interact directly with MPO since, at low concentrations, it inhibits MPO activity dose-dependently, with a 50% inhibitory effect reached close to 4lgmL1

In another study, hydroalcoholic extracts of *P. alata* showed antioxidant activity in rat liver slices. Iron initiates free radical oxidations, stimulating lipid peroxidation and inhibiting the function of various membrane proteins in vitro (Qian &Buettner, 1999). The inclusion of iron in the incubation medium of rat liver slices substantially increased cell death, generation of TBARS (Thiobarbituric acid reactive substances (TBARS) are formed as a byproduct of lipid peroxidation (i.e., as degradation products of fats), which can be detected by the TBARS assay using thiobarbituric acid as a reagent.) and protein carbonyl content. However, the co-incubation with *P. alata* or *P. edulis* leaf extracts at a concentration of 1μg/ml provided significant antioxidant protection to the rat liver slices, as evidenced by decreased lactate dehydrogenase (LDH) leakage [11].

In addition, while several studies investigating the antioxidant activity of extracts rich in polyphenols have focused on protective effects against lipid peroxidation, this study demonstrates that both *P. alata* and *P. edulis* leaf extracts have significant protective effects against carbonyl protein formation. This is particularly important since oxidized proteins are often functionally inactive, and oxidative stress may affect the activity of enzymes, receptors, and membrane transporters (Stadtman, 2001). Moreover, oxidized proteins are suggested to play a toxic role in the pathogenesis of several diseases, especially in neurodegenerative diseases [12].

Antiglycation activity

Proteins are modified by glucose through the glycation reaction, resulting in advanced glycation end-products (AGEs). The contribution of AGEs to diabetes, aging, and AlzheimerÕs disease have received considerable attention in recent years, and free radicals have been shown to participate in AGEs formation. It has been reported that antioxidants and radical scavengers inhibit these processes (Nakagawa, Yokozawa, Terasawa, Shu, & Juneja, 2002). *P. alata* leaf extracts showed protective effects against glucose-induced protein modifications, significantly inhibiting the AGEs formation. The mechanism of inhibition of AGEs formation by Passiflora extracts requires further investigation. Results were expressed as percentage inhibition of the formation of the glycated protein. The *P. alata* extract showed a significant inhibition of AGEs formation at 5 and 10 μg/ml concentrations [13-15].

Gastroprotective activity

P. alata acts as a gastroprotective agent based on its traditional use for gastric problems.

The *P. alata* yield after freeze-drying was 16%, and the total flavonoid content, expressed as vitexin, was 0.67% ± 0.0; this acts as a test solution.

Female Wistar rats weighing 150–180 g were used for this study. Test solutions of *P. alata* were administered by gavage (10 ml/kg). Thirty minutes after administering test samples,

lesions were induced by gavage of an HCl solution (necrotizing agent) in ethanol/water 60% (v/v) at doses of 10 ml/kg body weight. Ethanol stimulates endothelin-1 release from gastric vessels, resulting in vasoconstriction by interacting with ETA receptors. This process disturbs gastric microcirculation, which contributes to lesion formation. One hour later, the animals were killed in a CO_2 chamber. The stomachs were removed and opened along the greater curvature to determine the relative lesion area [16-18].

Lansoprazole (30 mg/kg standard was used as standard.

Using the necrotizing agent at 150 mmol/l, it was able to inhibit completely (1000%)the ulcer formation (compared to the negative control) for all tested dosages (100, 200, and 400 mg/kg), while lansoprazole (30 mg/kg) promoted 77% of inhibition. These results showed significant gastroprotective effect for PA in the model of acute gastric ulcer induced by HCl/ethanol

In the same assay, PA nano capsules exhibited more potent activity with 55%, 94%, and 90% inhibition for the respective doses of 25, 50, and 100 mg/kg. Maximum ulcer protection occurred at 50 mg/kg with the nano-encapsulated extract. These results suggest the potential use of *P. alata* as a gastroprotective herbal medicine [19-23].

Anti-diabetic activity

To study the anti-inflammatory properties of this extract in experimental type 1 diabetes, NOD mice were divided into two groups: the *P. alata* group, treated with aqueous extract of *P. alata* Curtis, and a non-treated control group, followed by diabetes expression analysis.

The consumption of aqueous extract and water ad libitum lasted 28 weeks. The treated group presented a decrease in diabetes incidence, a low quantity of infiltrative cells in pancreatic islets, and increased glutathione in the kidney and liver ($p < 0.05$) compared with the diabetic and non-diabetic control groups. In conclusion, the consumption of aqueous extract of *P. alata* may be considered a good source of natural antioxidants, and compounds found in its composition can act as anti-inflammatory agents, helping in the control of diabetes [24-27].

Antitumor activity

P. alata leaf extract (PaLE), consisting of flavonoid and saponins, are shown to exhibit this action synergistically. In vitro cytotoxic activity of Pale was assessed by the MTT method against four types of tumor cell lines PC-3, K-562, HepG2, and S180. It had indicated that *Pa*LE inhibits cell proliferation (CPI) > 75% against the four tested tumor cell lines and IC_{50} < 30 µg/mL for two tumor cell lines (PC-3 and S180). Development of anticancer drugs of pale against PC-3 and S180 was done because the IC_{50} value for these two was reported to be below 30 µg/mL.

Since *Pa*LE is cytotoxic for tumor cell lines, with insignificant activity against non-tumor cells, we have progressed to evaluate the antitumor activity in vivo, upon the intraperitoneally (i.p) and oral administration in an experimental S180 tumor mice model. No significant in

vivo antitumor activity was observed upon oral administration of the *Pa*LE. Hence i.p was chosen. Saline was used as a negative control. 5-FU 25 mg/kg/day and Cyclophosphamide 15 mg/kg/day (cycle) were used as positive control. It showed antitumor activity in treatments intraperitoneally (36.75% and 44.99% at doses of 100 and 150 mg/kg/day, respectively).

The leukocyte hematological parameters evaluated in animals treated with PaLE were the total leukocytes and differential count. Chemotherapeutic agents commonly cause hematological changes and, more specifically, leukopenia and percentage changes in the lymphocyte and neutrophil ratio in the differential count. This information was confirmed by Britto et al. A drastic decrease in the levels of total leukocytes and a change in the percentage ratio of lymphocytes and neutrophils were observed in the group treated with 5-FU. Consequently, animals treated with the 5-FU antineoplastic produced the same response pattern (Table 5), which explains the decrease in the size of the spleen. However, the test groups in our study, treated by i.p. with PaLE, demonstrated a significant increase in total leukocytes (leukocytosis) and a change in the percentage relationship between lymphocytes and neutrophils. No hemolytic activity was observed, usually in anticancer drugs [28].

Antimicrobial

The antimicrobial activity of acetone, ethyl acetate, and ethanol extract of *P. alata* (Dried ground plant) material was tested against 27 microorganisms, including 17 strains of bacteria and ten species of Fungi.

Antimicrobial activity was tested by determining the minimum inhibitory concentration (MIC) and minimum microbicidal concentration (MMC) by using the microdilution method with resazurin (Sarker et al., 2007). Resazurin 10 µL is a blue non-fluorescent dye that becomes pink and fluorescent when reduced to resorufin by oxidoreductases within viable cells. MIC was the lowest concentration of a tested substance that prevented resazurin color change from blue to pink.

Doxycycline and fluconazole, dissolved in a nutrient-liquid medium, were used as positive controls.The most potent antimicrobial activity was detected in G+ bacteria, while the activities on other species were moderate. Ethyl acetate extract showed the most potent effect, where the MIC for the G-species had an average value of 5 mg/ml, the MMC the value of 10 mg/ml, while for G+ bacteria, the average value was 1 mg/ml. *E. faecalis* ATCC 29212 is the strain where all extracts acted strongly with values below 0.156 mg/ml [29].

The antifungal activity was generally weak. In the tested species, the action on yeast was more expressed than on the filamentous fungi, where all the extracts had approximately the same efficacy (MIC from 2.5 to 20 mg/ml and MMC from 5 to 20 mg/ml). Ethyl acetate extract stood out with a more substantial effect on all the tested fungi than other extracts, with a noticeable difference ($p < 0.05$). All extracts showed the most decisive impact on preventing the development of *Rhodotorula sp.* (MIC at about 2.5 mg/ml, MMC at 5 mg/ml). In filamentous fungi, the influence of extracts was slightly more substantial on the species of the genus *Penicillium* [30].

This research suggests that *Passiflora alata* grown in special living conditions also has specific antimicrobial properties and biologically active substances.

CONCLUSION

This review shows that *Passiflora alata* is an important medicinal plant with a diversified phytochemical and pharmacological profile. The extensive literature investigation suggested a gap in the pharmacological and analytical profiles. Further studies on the detailed pharmacology through advanced animal models and analytical approaches are highly needed to understand the molecular mechanism underlying the reported activities. That will help justify the traditional use of the plant and can shed light on the natural product drug discovery.

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