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# Diplopterys pubipetala: review of traditional use, phytochemical and potential health benefits

Diplopterys pubipetala: revisão do uso tradicional, fitoquímico e potenciais benefícios à saúde

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## **ABSTRACT**

**Objective:** To compile and synthesize studies addressing the ethnobotanical and phytochemical characteristics of *D. pubipetala*. **Methodology:** A comprehensive literature

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search was conducted using databases such as Google Scholar, ScienceDirect, SciELO, Capes journals, and academic books, encompassing ethnobotanical, ethnopharmacological, and phytochemical data. Results: The species exhibits a Variety of secondary metabolites, including phenolic compounds, alkaloids, and terpenes. Its alkaloid profile resembles that of Banisteriopsis caapi, a principal component of Ayahuasca, which has demonstrated therapeutic potential. Notable antioxidant activity was identified in leaf and stem extracts, likely due to flavonoids. Additionally, in vitro studies revealed cytotoxic, anti-inflammatory, and anti-metastatic effects. **Conclusion:** Further investigation into the species' secondary metabolites is warranted to ensure safety and support the exploration of its pharmacological potential, particularly regarding antimicrobial, antifungal, and in vivo applications.

**Keywords:** *Diplopterys pubipetala*; *Banisteriopsis pubipetala*; Ayahuasca tea; Antioxidant activity; Anti-inflammatory action.

#### **RESUMO**

**Objetivo:** Compilar e sintetizar estudos abordando as características etnobotânicas e fitoquímicas de *D. pubipetala*. **Metodologia:** Uma busca bibliográfica abrangente foi conduzida usando bases de dados como Google Acadêmico, ScienceDirect, SciELO, periódicos Capes e livros acadêmicos, abrangendo dados etnobotânicos, etnofarmacológicos e fitoquímicos. **Resultados:** A espécie exibe uma variedade de metabólitos secundários, incluindo compostos fenólicos, alcaloides e terpenos. Seu perfil alcaloide assemelha-se ao de *Banisteriopsis caapi*, um dos principais componentes da Ayahuasca, que demonstrou potencial terapêutico. Notável atividade antioxidante foi identificada em extratos de folhas e caules, provavelmente devido aos flavonoides. Além disso, estudos *in vitro* revelaram efeitos citotóxicos, anti-inflamatórios e antimetastáticos. **Conclusão:** Investigações adicionais sobre os metabólitos secundários da espécie são necessárias para garantir a segurança e apoiar a exploração de seu potencial farmacológico, particularmente em relação às aplicações antimicrobianas, antifúngicas e *in vivo*.

**Palavras-chave:** *Diplopterys pubipetala*; *Banisteriopsis pubipetala*; Chá de Ayahuasca; Atividade antioxidante; Ação anti-inflamatória

## **INTRODUCTION**

The Malpighiaceae family is one of the most diverse, consisting of shrubs and vines predominantly found in neotropical regions of the Americas<sup>1,2</sup>. About 45 genera and 529 species are distributed in Brazil, especially in the Cerrado and Atlantic Forest biomes<sup>3</sup>. In this family, many genera are commonly explored for knowledge and to obtain bioactive



compounds that may serve as components with phytotherapeutic or medicinal utility<sup>4</sup>. The search for bioactive molecules of plant origin aligns with the success of drug development, as medicinal plants based on traditional knowledge are typically the initial source for chemical syntheses<sup>5</sup>.

The genus *Diplopterys* comprises 31 species in dry and humid tropical forests in the neotropics<sup>6,7</sup>. *Diplopterys pubipetala* (A.Juss.) W. R. Anderson & C. Davis (*Banisteriopsis pubipetala* (A. Juss.) Cuatrec.) is the species of interest in this review study. *D. pubipetala* belongs to the genus *Diplopterys* A. Juss., which, together with the genus *Banisteriopsis* C.B. Rob., are considered sister genera, both due to the similarity of floral structure<sup>6</sup> and molecular data analysis<sup>7</sup>. Thus, some materials selected in this investigation still bear the designation *B. pubipetala*.

Known as "cipó-preto, cipó-de-rego, or crista-de-galo"<sup>6</sup>; "tucunacá" in the Brazil North region<sup>8</sup>, and "marvaquero" by locals in the northern state of Minas Gerais, the vine *D. pubipetala* is one of the more than 1315 species belonging to the Malpighiaceae family<sup>9</sup>. It is widely distributed throughout Brazil, often found in forests and cerrados of the Espinhaço Range and Central Plateau, can reach up to one and a half meters in height, and presents itself as a climber when mature. Flowers develop in September, and November is the fruiting period<sup>3,10,11</sup>.

## **METHODOLOGY**

A comprehensive literature review on *Diplopterys pubipetala* was carried out using databases such as Google Scholar, ScienceDirect, SciELO, and Web of Science, in addition to specialized journals. The search included original research articles, review papers, and technical bulletins published between 1980 and 2024, with the objective of compiling data related to the ethnobotanical, ethnopharmacological, and phytochemical aspects of the species. The review was guided by specific descriptors, including the following terms and/or their combinations: "Malpighiaceae", "*Diplopterys pubipetala*", "*Banisteriopsis pubipetala*", "secondary metabolites", "phytochemistry", "bioactive compounds", "histochemistry", "chemical composition", "chemical compound", "antioxidant activity", "extract", and "natural substances". The exclusion criteria comprised conference abstracts, as well as theses and



dissertations that had not been published in peer-reviewed journals, even when falling within the time frame defined for this study.

## **Chemical composition - Histochemical tests**

In the leaf tissues of *D. pubipetala*, histochemical tests revealed a greater distribution of secondary metabolites, with flavonoids, alkaloids, and terpenes observed in the epidermis, periderm, and palisade parenchyma. In the stems, these classes were more evident in the epidermis. Commonly, calcium oxalate crystals were also observed in these tests<sup>12</sup>.

In the chemical analysis of species *Stigmaphyllon auriculatum*, *Stigmaphyllon ciliatum*, and *Stigmaphyllon paralias*, the metabolites present in common in leaves and aerial stems were quaternary alkaloids, condensed tannins, triterpenes, flavones, and flavonols. Saponins and quinones were limited to *S. ciliatum* and *S. paralias*. Resins were identified only in *S. auriculatum*. Chalcones and aurones were common in the underground parts of the three species investigated<sup>13</sup>.

It was verified through histochemical tests of the leaf blade that hydrophilic components, including polysaccharides and reducing sugars, are present, and that in the outermost layer of the cuticle of *D. pubipetala* it reacts to the presence of lipids, while the inner layer contains pectin and mucilages<sup>14</sup>. The leaf and calyx glands of *Banisteriopsis campestris*, *Banisteriopsis laevifolia*, and *Banisteriopsis malifolia* produce secretions<sup>15</sup> determined by a mixture of proteins, lipids and polysaccharides.

The histochemical tests<sup>11</sup> in fresh wood from the stem and bark of *D. pubipetala* revealed mainly the presence of alkaloids, phenolic compounds, tannins and terpenoids from essential oils were also found, while saponins were barely noticeable in the bark and wood.

Histochemical analyses of mature caliciform glands revealed the excretion of phenolic substances, polysaccharides, and proteins into the subcuticular space of elaiophores<sup>16</sup>. The presence and accumulation of lipid content in this subcuticular space have also been reported in Malpighiaceae species: *Banisteriopsis sericea*, *Dinemandra ericoides*, *Heteropterys chrysophylla*, *Malpighia coccigera* and *Peixotoa hispidula*<sup>15</sup>.

## Chemical composition of flowers

In general, lipids are present in the cuticles of the calyx, corolla, and androecium glands; proteins, pectin, mucilages, polysaccharides, and phenolics are found in the epidermis



of these glands; these substances were also detected in the cell walls except for proteins; terpenes are only present in the epithelial cells of the corolla and staminal glands; translucent and slightly viscous exudates, which are mucilages and polysaccharides, appear on the surface of the connective tissue of the androecium glands<sup>16,17</sup>. The floral odors, of lipophilic nature, produced by the osmophores present in the petal glands, were perceived through positive color reaction and ultrastructural analysis<sup>16</sup>. For species of *Byrsonima gardneriana*, *Byrsonima coccolobifolia*, and *Byrsonima verbascifolia*, it was found that the flowers do not have a perceptible odor and remain receptive for two days in the case of the first two species, while the last species remains receptive for about 72 hours<sup>18</sup>.

The variation in the chemical composition of floral oils was observed in some species<sup>19</sup>, *Peixotoa tomentosa* contains acylglycerols available at the peak of the dry season, while for the species *B. campestris* and *B. malifolia*, the highest abundance occurred in the rainy period of summer, with a highlight on disubstituted fatty acids. In the case of the species *Pterandra pyroidea*, based on gas chromatography and mass spectrometry analysis, the fatty acid detected in greater quantity as a methyl ester derivative in floral oils was 5,7-diacetoxidocosanoic acid<sup>20</sup>. For the species *Byrsonima intermedia*, the major component of floral oil is the isomer of the previously mentioned acid, described as byrsonic acid<sup>21</sup>. Tricosanoic acid, palmitic acid, and heneicosanoic acid were the main constituents of the floral oil discovered in *B. sericea*<sup>22</sup>.

## Seeds composition

Phenolic substances are present in the seed layers of *D. pubipetala*, as well as in the mature fruit, whose structure is lignified and also contains pectic substances<sup>23</sup>. The embryonic reserve of *D. pubipetala* is primarily composed of lipids, with scattered starch grains and numerous druses. Developing seeds exhibit an outer epidermis formed by cells with a high density of phenolic compounds<sup>24</sup>. Two studies refer to the fatty acid composition of the seeds: Pinho et al. (2009)<sup>25</sup> and the more recent one, Prazeres et al. (2017)<sup>26</sup>. In the former, analysis was conducted using gas chromatography coupled with electron impact mass spectrometry; whereas in the latter, it was performed through gas chromatographic analysis (headspace technique) coupled with mass spectrometry.

Both studies found a predominance of unsaturated fatty acids in the seeds, reaching 71.0% in the first investigation. The quantity of linoleic acid (C18:2) prevailed, being 42.8% <sup>25</sup>



and  $39.2\%^{26}$ . Other unsaturated fatty acids included linolenic acid (C18:3) (21.1%) and palmitoleic acid (C16:1) (7.11%)<sup>25</sup>, although oleic acid (C18:1) was not observed in the former study, where it was the second most abundant (32.6%) in the more recent one. Saturated fatty acids were also prominent, with palmitic acid (C16:0) at  $17.6\%^{25}$  and  $25.7\%^{26}$ .

The acids found in higher quantities in *D. pubipetala* seeds also correspond to those present in acerola seeds, *Malpighia glabra*. Linoleic acid, considered essential, is a substance not produced by animals; it is a valuable nutrient for the human diet. Although it has recognized nutritional value in many aspects as a precursor to hormones like prostaglandins and its involvement in physiological processes related to the prevention and treatment of cardiovascular diseases, diabetes, arthritis, and various inflammatory diseases, there remain contradictory issues regarding the ideal dietary levels to avoid adverse effects on human health<sup>27,28,29</sup>. The other fatty acid, however, saturated, is palmitic acid, which can be useful in cosmetic formulations, biodiesel production, among other applications<sup>27</sup>.

#### *Minerals*

The therapeutic effects demonstrated by medicinal plants are related to the peculiarities of their chemical composition, not only of the physiologically active substances they synthesize and accumulate, but also of the different classes of secondary metabolites—such as alkaloids, phenolics, terpenoids, and others—as well as the comprehensive profile of macro- and microelements of biological relevance<sup>30</sup>.

Seeds of *D. pubipetala* were investigated for the composition of the minerals sodium, potassium, calcium, magnesium, iron, copper, chromium, and aluminum (Na, K, Ca, Mg, Fe, Cu, Cr, Al) using high-resolution continuum source atomic absorption spectrometry, and for phosphorus (P), the colorimetric method of vanadomolybdophosphoric acid was used<sup>31</sup>.

The elements Cu, Cr, and Al did not reach the detection limit; all were below 0.11  $\mu g.g^{-1}$ . The most abundant macroelement was K ( $1636 \pm 135 \ \mu g.g^{-1}$ ), while the quantity of the trace element Fe ( $3.69 \pm 0.03 \ \mu g.g^{-1}$ ) compared to other investigated seeds was relatively low. The others, in descending order, are Mg ( $447 \pm 13 \ \mu g.g^{-1}$ ), P ( $288 \pm 55 \ \mu g.g^{-1}$ ), Ca ( $134 \pm 6 \ \mu g.g^{-1}$ ), and Na ( $38 \pm 1 \ \mu g.g^{-1}$ )<sup>31</sup>.

The homeostasis of metallic ions is essential for plant development, and the careful regulation of processes is crucial to avoid deficiencies or toxicity of metallic ions. Therefore, there is a constant need to acquire each nutrient that meets the requirements of this dynamic



process, which involves mobilization, absorption, and distribution within the plant, intracellular trafficking, and storage, as well as redox activities, with emphasis on Fe, Cu, and  $Cr^{32}$ .

Minerals are relevant concerning physiological and environmental importance; they play a role in maintaining and restoring health. Deficits in intake can lead to an increase in diseases and can serve as indicators of environmental contamination. The data obtained can also contribute to understanding the relative potential for human and animal consumption in the form of dietary supplements<sup>31,33</sup>.

In this regard, literature reports mineral quantification in maturing acerola fruit (M. glabra), with potassium (K) being prominent (150.43 mg.100g<sup>-1</sup>), similar to the findings in D. pubipetala seeds. This is followed by magnesium (Mg) (16.57 mg.100g<sup>-1</sup>), calcium (Ca) (12.90 mg.100g<sup>-1</sup>), iron (Fe) (7.06 mg.100g<sup>-1</sup>), and sodium (Na) (7.56 mg.100g<sup>-1</sup>)<sup>33</sup>. For green fruits<sup>34</sup> of M. emarginata, noteworthy results were also related to the presence of potassium (K) (2414.20  $\pm$  0.01 mg.100g<sup>-1</sup>) and calcium (Ca) (518.69  $\pm$  12.27 mg.100g<sup>-1</sup>) in the white flower variety. For other macrominerals (Ca, K, Mg, and Na), concentrations in the three investigated varieties generally ranged from 0.86  $\pm$  0.02 to 2414.14  $\pm$  0.01 mg.100g<sup>-1</sup>, while for microminerals (Mn, Cu, Fe, and Zn), values varied from 0.21  $\pm$  0.03 to 4.15  $\pm$  0.21 mg.100g<sup>-1</sup>, with white flower again having the highest quantities.

Phytochemical and chromatographic screening test

The phytochemical investigation of the hydroethanolic extract from leaves and stems of *D. pubipetala* revealed the presence of compounds that may contribute to the medicinal potential of this plant, whether as anti-inflammatory, antimicrobial, or antioxidant agents. Among the constituents are flavonoids, glycosylated flavonoids, alkaloids, tannins, terpenes, and prenylated xanthones<sup>12</sup>. Consistent with this investigation, another study on ethyl acetate, dichloromethane, and butanol partitions of leaves and stems in *D. pubipetala* identified five distinct classes of secondary metabolites: alkaloids, flavonoids, terpenoids, saponins, and lactones, consisting of 10 identified components<sup>35</sup>.

For three species of *Banisteriopsis* (*B. stellaris*, *B. adenopoda*, *B. argyrophylla*) in areas of the Cerrado, under different climatic seasons and developmental stages, the concentration of tannins was compared over two years of study. The highest amount was



present in old leaves during the dry season, which is related to leaf exposure time and water stress<sup>36</sup>.

Similarly, chromatographic analysis<sup>12</sup> revealed that the major components contained in the ethyl acetate partition obtained from the hydroethanolic extract of stems and leaves were consistent, although the latter presented double the number of substances evidenced by peaks. Analysis of the absorption spectra allowed the inference that three compounds belong to the same class of secondary metabolites. The absorption of ultraviolet light between 320 and 385 nm is attributed to the B-ring of the benzene structure, while a second absorption band between 250 and 285 nm corresponds to the A-ring, which is characteristic of flavones and flavonols<sup>37</sup>. Further consistent with these findings, it was found that there is a higher concentration of these substances in the leaf than in the stem, thus aligning with the result presented in the phytochemical investigation<sup>12</sup>.

Through direct infusion analysis in electrospray ionization (ESI), the provisional identification of eight substances belonging to the crude hydroethanolic extract of leaves and stems was obtained. The substances were detected by ESI(+) positive mode (protonated form  $[M + H]^+$  and/or as sodium adducts  $[M + Na]^+$ ), or in the deprotonated form  $[M - H]^-$ , ESI(-) negative mode, with four of them common to both extracts<sup>12</sup> namely: hexose (C<sub>6</sub>H<sub>12</sub>O<sub>6</sub>), haematomatte (C<sub>9</sub>H<sub>8</sub>O<sub>5</sub>), dambonitol (C<sub>8</sub>H<sub>16</sub>O<sub>6</sub>), and verticoglucuronic acid (C<sub>15</sub>H<sub>18</sub>O<sub>10</sub>).

The other substances with relative intensity in the leaf extract were: 1-isomangostin and/or 3-isomangostin ( $C_{24}H_{27}O_6$ ); mangostenol and/or mangostanol ( $C_{24}H_{27}O_7$ ); apigenin, galangin, and/or glycosylated genistein ( $C_{21}H_{20}O_{10}$ ); glycosylated kaempferol ( $C_{24}H_{16}O_9$ )<sup>12</sup>.

Cucurbitin A  $(C_{29}H_{28}O_{11})$ , syringetin 3-glucuronide  $(C_{23}H_{22}O_{14})$  and macarangaflavanone  $(C_{25}H_{28}O_5)$  were identified in the ethyl acetate leaf partitions and the latter of them in butanol. Among the described actions for syringetin 3-glucuronide are antioxidant, anti-allergic, and anti-inflammatory; and for macarangaflavanone A, antimicrobial activity is described<sup>35</sup>.

The substance kaempferol was also the subject of study, as well as quercetin and catechin belonging to the ethanolic extract of *B. argyrophylla* leaves, in which 10 flavonoids with biological activity were identified<sup>38</sup>, and in another study, bioactive compounds such as procyanidins and megastigmane glycosides were identified<sup>39</sup>.



In the ethanolic extract of leaves and flowers of *B. laevifolia*, through high-performance liquid chromatography coupled with tandem mass spectrometry, 7 compounds reported for the first time were identified, including flavonoids and terpenoids<sup>40</sup>. The phytochemical screening<sup>41</sup> of this species also indicated the presence of phenols, steroids, sugars, and tannins.

Regarding the terpenes of *D. pubipetala*, phytuberin ( $C_{17}H_{26}O_4$ ) stood out, which was identified in all leaf partitions and in the stem partition of dichloromethane, with antimicrobial and antifungal actions<sup>35</sup>. Additionally, ginsenoside Rh2 ( $C_{36}H_{62}O_8$ ) was identified in the butanol leaf partition, a molecule considered important as it can inhibit glutamate action and possesses anti-obesity properties and risk factors reducers for metabolic diseases such as diabetes<sup>35</sup>.

Alkaloids were more evident in the more polar partition (butanol), among them are: N-cis-feruloyltyramine ( $C_{18}H_{19}NO_4$ ) with potential anticarcinogenic, anti-inflammatory, antioxidant, and antifungal biological activity; and the alkaloid simulansamide ( $C_{22}H_{23}NO_6$ ) capable of inhibiting platelet aggregation<sup>35</sup>.

Although alkaloids are present in several Malpighiaceae species, they are predominantly restricted to vine genera such as *Banisteriopsis*, *Diplopterys*, *Tetrapterys*, and *Stigmaphyllon*<sup>36,42</sup>. The widespread occurrence of alkaloids in Banisteriopsis and related genera like *Diplopterys* supports the diversity of plant species used in the preparation of Ayahuasca tea<sup>11</sup>. This also highlights the challenge in distinguishing among users, who often collect and utilize different species interchangeably, given the similar hallucinogenic effects elicited by these alkaloids.

## Ethnobotanic aspects: Ayahuasca tea

The Ayahuasca tea is characterized by the psychoactive effects caused by the synergistic interaction between alkaloids present in the bark and stems of *B. caapi* (Spruce ex Griseb.) Morton (Malpighiaceae) and the leaves of the species *Psychotria viridis* Ruiz & Pav. (Rubiaceae)<sup>43</sup>. It is known that other species of *Banisteriopsis* can also replace the *B. caapi* species in a similar way, and *D. pubipetala*, by presenting several similarities with the genus, has also been explored and referred to as "Ayahuasca analogue," as it represents a non-traditional combination with the same active principle<sup>11,8</sup>.



Studies on the bioactive properties of Ayahuasca tea associate it with beneficial effects in various physical and psychological conditions, particularly in the treatment of depression, anxiety, and various neurobiological diseases such as degenerative diseases, severe physical illnesses, cancer, chronic conditions, post-traumatic stress disorders, personality disorders, Parkinson's, and Alzheimer's diseases, as well as possessing anti-inflammatory and antimicrobial properties, demonstrating its therapeutic potential<sup>44</sup>.

Research conducted with 176 vegetal lianas, including 159 samples of *B. caapi* and 33 samples of Ayahuasca, aimed to verify the presence of  $\beta$ -carboline alkaloids in this infusion. Only one sample out of the five samples of *D. pubipetala* contained  $\beta$ -carbolines, with 0.16 mg.g<sup>-1</sup> of harmine, 0.046 mg.g<sup>-1</sup> of harmaline, and 1.04 mg.g<sup>-1</sup> of tetrahydroharmine. The other four samples from the central region of Brazil possibly affected by factors related to environmental conditions, organic and inorganic soil composition, and the biosynthesis of these compounds did not have detectable minimum amounts (LOD) and values below 0.0009 mg.g<sup>-1</sup>, 0.0018 mg.g<sup>-1</sup>, and 0.0146 mg.g<sup>-1</sup>, respectively<sup>48</sup>.

## Quantification of phenolic compounds

Phenolic compounds in the hydroethanolic extracts of leaves and stems of D. pubipetala were quantified using the Folin-Ciocalteu method. The results were expressed in mg GAE.g<sup>-1</sup> (milligrams of gallic acid equivalent per gram of extract) obtained by interpolation of the sample absorbance relative to the calibration curve, resulting in 146.09  $\pm$  3.31 mg GAE.g<sup>-1</sup> and 100.19  $\pm$  9.26 mg GAE.g<sup>-1</sup>, respectively, with the leaf and stem extract showing nearly 50% higher value<sup>12</sup>.

For *B. laevifolia*, phenolics quantification resulted in 288.67  $\pm$  0.04 mg GAE.g<sup>-1</sup> (ethanolic extract of flowers) and 225.67  $\pm$  0.07 mg GAE.g<sup>-1</sup> (ethanolic extract of leaves)<sup>40</sup> In the same species, reported<sup>41</sup> 542.0  $\pm$  2.1 mg GAE.g<sup>-1</sup> for the ethanolic leaf extract and 784.7  $\pm$  5.6 mg GAE.g<sup>-1</sup> for the n-butanol partition, with the ethyl acetate partition also noteworthy at 660.0  $\pm$  1.5 mg GAE.g<sup>-1</sup>.

For the ethanolic leaf extract<sup>39</sup> of *B. argyrophylla*, the total phenolics content was  $337.1 \pm 1.4$  mg GAE.g<sup>-1</sup>. For *B. gardneriana*, values obtained were  $425.105 \pm 8.523$  mg GAE.g<sup>-1</sup> for the crude extract and the highest content of  $509.947 \pm 7.387$  mg GAE.g<sup>-1</sup> for the ethyl acetate fraction, followed by the butanol ( $492.261 \pm 4.904$  mg GAE.g<sup>-1</sup>),



trichloromethane (243.29  $\pm$  3.897 mg GAE.g<sup>-1</sup>), and hexane (80.42  $\pm$  0.693 mg GAE.g<sup>-1</sup>) fractions<sup>49</sup>.

Phenolic antioxidants can act by molecularly altering free radicals to neutralize them, chelating metals, and hindering the initiation and propagation steps of lipid peroxidation<sup>50</sup>. These abilities are related to the structural heterogeneity of phenolic compounds found in plants, which allow variable solubility in organic solvents and water, enabling various actions in plants such as defense against pathogens and herbivores, attraction to pollinators or fruit dispersers, and allelopathic effects<sup>51</sup>. For human health, the antioxidant power of these phenolic compounds contributes to the body's defenses, potentially affecting various important pathological pathways, including cardiovascular diseases, neurodegenerative diseases, diabetes, inhibition or retardation of cancer cells, and slowing down the aging of cells in general<sup>52,53</sup>.

## Quantification of flavonoids

The quantification of total flavonoids was also carried out for the leaf and stem extracts of *D. pubipetala*, and the concentrations obtained were expressed in mgQ.g<sup>-1</sup> or mgR.g<sup>-1</sup> (mg of quercetin equivalent per gram of extract or mg of rutin equivalent per gram of extract) namely:  $20.25 \pm 0.39$  mgQ.g<sup>-1</sup> and  $88.15 \pm 4.41$  mgR.g<sup>-1</sup> for leaf extract, and  $7.75 \pm 0.45$  mgQ.g<sup>-1</sup> and  $23.09 \pm 4.56$  mgR.g<sup>-1</sup> for stem extract<sup>12</sup> These values are consistent with the higher phenolic content obtained for the leaf extract compared to the stem extract. Such values were low when compared to those obtained for B. laevifolia:  $199.87 \pm 0.13$  mgAG.g<sup>-1</sup> (mg of gallic acid equivalent per gram of extract) for flower extract and  $173.30 \pm 0.08$  mgAG.g<sup>-1</sup> for leaf extract, expressed<sup>40</sup> in mgAG.g<sup>-1</sup> whereas in a previous study<sup>41</sup>, obtained  $61.2 \pm 0.4$  mgQ.g<sup>-1</sup> for the crude leaf ethanol extract, with the partitions with higher values being  $88.8 \pm 3.5$  mgQ.g<sup>-1</sup> for ethyl acetate and  $77.2 \pm 1.8$  mgQ.g<sup>-1</sup> for dichloromethane.

As for the values obtained for the extract and fractions of *B. argyrophylla*, they were very close in the ethanol extract and hexane fraction (71.8  $\pm$  0.3 mgQ.g<sup>-1</sup> and 71.0  $\pm$  1.9 mgQ.g<sup>-1</sup>, respectively). Among the other fractions, the highest highlight, as with *B. laevifolia*, was reserved for the ethyl acetate fraction 211.9  $\pm$  2.9 mgQ.g<sup>-1</sup>, which surpassed all the previous ones<sup>39</sup>.



### **Antioxidant activity**

The EC<sub>50</sub> (efficiency concentration) values of the leaf and stem extracts of *D. pubipetala* were respectively 25.42 μg.mL<sup>-1</sup> and 50.73 μg.mL<sup>-1</sup>, while the calculations for the AAIs (antioxidant activity indices): 1.6 and 0.79 respectively demonstrated that the antioxidant activity of the hydroethanolic leaf extract is excellent while for the stems it is moderate. These values corroborate with the previous quantifications, as the increased antioxidant potential is attributed to samples with a higher presence of phenols and flavonoids<sup>12</sup> In this study, the DPPH (2,2-difenil-1-picrilhidrazil) radical method was used, in which the EC<sub>50</sub> value (concentration required to inhibit the DPPH radical by 50%) was obtained from spectrophotometric reading at 517 nm.

Antioxidant activity using the DPPH radical method was also measured for leaf extract and fractions of *B. laevifolia*. Among the values obtained, it can be highlighted that the ethanolic leaf extract  $107.21 \pm 0.09 \, \mu g.mL^{-1}$  was not as good as that of the flowers  $24.38 \pm 0.07 \, \mu g.mL^{-1}$ , which was compatible with the standard substance used, and all subfractions had values considered moderate<sup>40</sup> Still for this species, the investigation<sup>41</sup> carried out obtained EC<sub>50</sub> for the ethanolic extract  $4.5 \pm 0.9 \, \mu g.mL^{-1}$  and for the ethyl acetate partition resulted in  $4.1 \pm 0.5 \, \mu g.mL^{-1}$ , these values were very close to that obtained for the standard substance used (butylated hydroxytoluene), therefore classified as relevant. This same test was performed for the leaf extract and partitions of *B. argyrophylla* and the most significant results occurred in the ethyl acetate partition  $4.1 \pm 0.1 \, \mu g.mL^{-1}$ , followed<sup>39</sup> by the ethanolic extract  $4.3 \pm 0.8 \, \mu g.mL^{-1}$  and the butanol partition  $4.8 \pm 0.8 \, \mu g.mL^{-1}$  The best antioxidant activity for the species *B. gardneriana* occurred with the ethyl acetate phase  $(3.45 \pm 0.043 \, \mu g.mL^{-1})$ , followed by the n-butanol phase  $(3.840 \pm 0.005 \, \mu g.mL^{-1})$  with values similar to or close to the standard substance<sup>49</sup>.

Overall, the results obtained for the extracts or partitions analysed have better antioxidant activity values in those with a higher presence of flavonoids and phenolics, directly related to the polarity of the sample. More specifically, there is the possible addition of the synergistic effect promoted by the structure of the catechol group present in the hydroxyl group of the B ring, which can donate hydrogen to stabilize the radical, since the crude ethanolic extracts also had promising results <sup>12,41,49</sup>.



### In vitro antitumor activity

In a pioneering study<sup>54</sup>, substances from the ethyl acetate partition of the hydroethanolic extract of leaves and stems were separated through classic liquid chromatography and tested *in vitro* on B16-F10 melanoma cell line to evaluate their antitumor activity. The partitions were directed towards the class of flavonoids, as it is described in the literature that they contain the ability to inhibit the rapid growth of melanoma, induce apoptosis, and stimulate antitumor immunity in the organism.

Cell proliferation measurement and cytotoxicity for the investigated fractions reduced over 50% of B16-F10 cell viability at a concentration of 125  $\mu g.mL^{-1}$ . In contrast, other species widely used as chemotherapeutic agents were unable to reduce 50% of cell viability of different cancer cell lines at doses lower<sup>54</sup> than 125  $\mu g.mL^{-1}$ .

Regarding cell migration, it was strongly inhibited, yielding interesting results. It is known that this phenomenon prompts the need for further studies, as such characteristics can lead to the advancement of new strategies and approaches for treating this disease. In this investigation, only one of the fractions generated effects similar to the control, and therefore, was considered irrelevant compared to the others which were able to inhibit the metastatic action of melanoma cells, decrease viability, migration capacity, and cause death of B16-F10 tumor cells<sup>54</sup>.

In another study<sup>55</sup>, plants had their leaf, stem, and fruit extracts investigated against B16-F10 (mouse melanoma), HepG2 (human hepatocellular carcinoma), K562 (human chronic myelocytic leukemia), and HL-60 (human promyelocytic leukemia) tumor cell lines. The results for the inhibitory effects on growth from extracts/fractions of *B. sericea* make it promising for the development of anticancer drugs, as the values obtained for the ethyl acetate, methanol, and hexane fractions were lower than the reference value inhibitory concentration (IC<sub>50</sub>) less than 30 μg.mL<sup>-1</sup>.

The aqueous extract of acerola fruit (*M. glabra*) was investigated for its effects on melanogenesis in B16 mouse melanoma cells, which significantly reduced cellular melanin levels and inhibited tyrosinase activity in a concentration-dependent manner. It also showed potent antioxidant activity. In human patch tests, no allergic reaction was observed with the presented results. Estimate the possibility<sup>56</sup> that the aqueous extract of the fruit may be part of the composition of anti-aging foods and skin-lightening cosmetics.



Another Malpighiaceae, *Flabellaria paniculata* Cav., was investigated for the treatment and prevention of breast cancer, specifically in West Africa, where traditional practices already involve the use of the roots of this plant. In that study<sup>57</sup>, some compounds were isolated and purified from the crude extract and fractions. Among the results, it was observed that *in vitro*, the phytosterols: campesterol glucoside with  $IC_{50}$  1.18  $\pm$  0.18 mg.mL<sup>-1</sup> and sitosterol with  $IC_{50}$  1.79  $\pm$  0.14 mg.mL<sup>-1</sup> were more active than the flavonoid quercetin  $IC_{50}$  2.05  $\pm$  0.16 mg.mL<sup>-1</sup>; although the activities are lower when compared to the standard anticancer drug Paclitaxel ( $IC_{50}$  0.07  $\pm$  0.03 mg.mL<sup>-1</sup>). Among the tested fractions on breast cancer cells, the most active was the hexane fraction (0.97  $\pm$  0.05 mg.mL<sup>-1</sup>), followed by the ethyl acetate fraction (2.97  $\pm$  0.19 mg.mL<sup>-1</sup>), aqueous (4.10  $\pm$  0.13 mg.mL<sup>-1</sup>), and butanol (6.22  $\pm$  0.17 mg.mL<sup>-1</sup>).

## Potential anti-inflammatory and cytotoxic

The anti-inflammatory and cytotoxic potential, *in vitro*, was also evaluated for the ethyl acetate and dichloromethane fractions of *D. pubipetala* leaves. The extracts were tested for their effects on the production of cytokines IL-6 (interleukin-6), IL-10 (interleukin-10), TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ). Additionally, the quantification of nitric oxide levels was performed since it is known to act as a modulator in pathological processes<sup>37</sup>.

Cell viability was tested using 3T3 cells (mouse embryonic fibroblast cell lines), and the extracts were found to be cytotoxic. The difference in cell viability between the solvent of the partition was  $IC_{50}$  67.39  $\mu g.mL^{-1}$  for dichloromethane and 103.37  $\mu g.mL^{-1}$  for the ethyl acetate extract. This result indicated that the 3T3 cells were more sensitive to the dichloromethane solvent, suggesting that this partition carries more cytotoxic compounds compared to the ethyl acetate partition<sup>37</sup>.

From this MTT (tetrazoline 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl bromide) assay, it was observed that the pro-inflammatory cytokines IL-6 and TNF- $\alpha$  had significantly decreased production in both partitions, with reductions of 45.1% and 40.4% for IL-6, and 35.7% and 32.9% for TNF- $\alpha$ , respectively, in the dichloromethane and ethyl acetate partitions<sup>37</sup>. These results are important since the concentrations used for these partitions were lower than the IC<sub>50</sub> determined in the cytotoxicity tests.



Conversely, in cells treated with these partitions, the levels of the anti-inflammatory cytokine IL-10 were increased, with values of 86.4% for the dichloromethane partition and 78.4% for the ethyl acetate partition compared to the control group.

The production of nitric oxide was particularly increased in 3T3 cells treated with the dichloromethane and ethyl acetate partitions. Using the Griess reaction, values of 291.7% and 316.7% were obtained, respectively, which were higher than the control group (untreated cells). These values, associated with changes in the quantities of pro-inflammatory and anti-inflammatory cytokines, are related to the immunomodulatory capacity promoted by the investigated partitions. This fact is attributed to the presence of flavonoids, which are secondary metabolites that act on the anti-inflammatory response and interfere with the production of cytokines such as TNF- $\alpha$ , as well as modulate the enzyme nitric oxide synthase  $^{37,58}$ .

In the same context, when reporting the anti-inflammatory activity in animal models involving the aqueous extract of B. intermedia leaves, a potent anti-inflammatory activity was observed with the reduction of paw edema, attributed to the presence of catechin and flavonoids<sup>59</sup>. These substances are essential to produce inflammatory mediators such as cytokines and prostaglandins. In the study involving the butanolic fraction of B. verbascifolia leaves, a pronounced anti-inflammatory effect was observed, which may be caused by the inhibition of the release of mediators derived from polymorphonuclear leukocytes<sup>60</sup>, TNF- $\alpha$ , and prostaglandin  $E_2$ .

Flavonoids and phenolic compounds, in general, are attributed with analgesic, antioxidant, and anti-inflammatory functions in extracts from plants of the genus *Byrsonima*. However, studies related to cytotoxicity are scarce, and the results obtained so far imply a high cytotoxic potential. Nevertheless, there has been no investigation into which compounds present in these species would have therapeutic importance. Therefore, chemical characterization can help in understanding the different potentialities of these and other plant species<sup>55,61</sup>.

#### **CONCLUSIONS**

The research discussed in this review focuses on the chemical aspects, as well as in



*vitro* initiatives related to the action of components present in extracts, partitions, and fractions of leaves and stems of *D. pubipetala* that may act on cancerous and inflammatory processes. Histochemical tests on the leaves, stems and bark showed the presence of flavonoids, alkaloids and terpenes, while in the flowers the presence of lipids in general stood out and, in the seeds, the unsaturated fatty acids stood out.

The literature points out that the varied mineral composition is closely related to other species in the family. Among the metabolites, it is considered that the presence of alkaloids, although not constant, justifies their use in the composition of Ayahuasca tea, which provides benefits in relation to neurodegenerative diseases. Possibly the excellent antioxidant capacity obtained for the leaves and related stems is the quantification of flavonoids and phenolics which are high.

There is still a noticeable lack of studies focusing on the chemical and pharmacological aspects related to the isolation and characterization of secondary metabolites to assess the safety and efficacy of using this species. It was noted other Malpighiaceae species are emerging as potential producers of bioactive compounds, highlighting the need for further research in this area.

## **Declaration of competing interest**

The authors declare that they have no competing financial interests or known personal relationships that could have appeared to influence the work reported in this article.

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