



Bioactive compounds associated with medicinal infusions and phytochemical preparations from Brazilian Cerrado plants: phytochemical diversity and structural elucidation

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Abstract The Brazilian Cerrado represents one of the world's most biodiverse savanna ecosystems and harbors a rich reservoir of medicinal plant species traditionally used in the preparation of aqueous infusions and decoctions. This review provides a critical and comparative assessment of traditional aqueous preparations and complementary phytochemical studies involving four emblematic Cerrado species: *Dipteryx alata* Vogel, *Hancornia speciosa* Gomes, *Bowdichia virgilioides* Kunth, and *Eugenia dysenterica* DC. The available evidence derives from heterogeneous preparation systems, including traditional aqueous infusions, hydroethanolic and methanolic extracts, chromatographically fractionated preparations, isolated compounds, formulation-based systems, and metabolomics-oriented analytical approaches. Across these systems, more than 80 metabolites have been reported, including flavonoids, isoflavonoids, phenolic acids, proanthocyanidins, galloylated derivatives, and prenylated chalcones, characterized using LC–MS/MS, HPLC–DAD, GC–MS, PS-MS, and one- and two-dimensional NMR spectroscopy. The reviewed studies suggest antioxidant, anti-inflammatory, hypoglycemic, antimicrobial, cytoprotective, antinociceptive, and neuropharmacological potential associated with proposed modulation

of pathways involving NF- κ B, AMPK, COX-related mediators, α -glucosidase, oxidative stress responses, and inflammatory signaling. Comparative structure–activity interpretations further suggest that prenylated and galloylated substituents may contribute to enhanced lipophilicity, membrane interaction, and biological responsiveness. However, the current evidence remains fragmented due to heterogeneous extraction methodologies, limited pharmacokinetic and toxicological characterization, insufficient standardization of preparations, and the scarcity of clinically relevant validation studies. This review highlights the importance of integrating ethnobotanically realistic aqueous preparations with metabolomics, bioassay-guided fractionation, and advanced analytical platforms to better understand which metabolites are genuinely associated with the traditional medicinal use of Cerrado species and their potential biotechnological applications.

Keywords Cerrado · Bioactive compounds · Flavonoids · Medicinal infusions · Secondary metabolism

Introduction

The Brazilian Cerrado is recognized as one of the most biodiverse biomes on the planet, often referred to as

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the “cradle of waters” due to its strategic role in water conservation and in supplying the major river basins of South America (de Castilho Silva et al. 2024). Covering approximately 2 million km², the Cerrado spans a vast area of central Brazil and extends into parts of neighboring countries, making it the second largest biome in Brazil. It is primarily distributed across the states of Goiás, Mato Grosso, Mato Grosso do Sul, Tocantins, Minas Gerais, Bahia, Maranhão, Piauí, and the Federal District (Furley 1999; IBGE 2020).

This biome harbors an exceptional diversity of plant species, many of them endemic and possessing unique phytochemical profiles. The complex chemical composition of Cerrado flora has attracted increasing scientific interest, particularly regarding its potential as a source of structurally diverse and pharmacologically active secondary metabolites. Several classes of compounds have been reported, including flavonoids, tannins, alkaloids, terpenoids, saponins, phenolic acids, steroids, and lignans (Gurib-Fakim 2006; Neto et al. 2020).

Historically, medicinal plants have played a central role in traditional Brazilian medicine, especially among Indigenous communities and rural populations (Leonti and Casu 2013). The empirical knowledge accumulated over generations has guided recent scientific investigations, particularly concerning the popular use of “medicinal teas” from the Cerrado, which are prepared by infusion or decoction of plant parts such as leaves, bark, roots, and fruits (Tabajara de Oliveira Martins et al. 2019). These preparations are widely used in the treatment of inflammatory, gastrointestinal, respiratory, infectious, metabolic, and degenerative conditions (de Carvalho et al. 2020).

Despite the growing interest, significant gaps remain in the scientific literature. The comprehensive identification of bioactive compounds, their mechanisms of action, and the potential synergistic effects resulting from metabolite interactions are still under-explored. Furthermore, there is a lack of systematic studies addressing optimal extraction conditions, chemical stability, and purification methods that would allow for the maximization of therapeutic compound recovery and utilization.

In recent years, advances in high-resolution analytical techniques—such as ultra-high performance liquid chromatography coupled with tandem mass spectrometry (UHPLC-MS/MS), gas chromatography–mass spectrometry (GC-MS), high-performance

liquid chromatography with diode array detection (HPLC–DAD), and one- and two-dimensional nuclear magnetic resonance (NMR) spectroscopy—have enabled more precise chemical characterization, opening new possibilities for the identification of novel compounds and the validation of their bioactive properties (Queiroz et al. 2024; Meunier et al. 2024).

In this context, the present review aims to provide a critical, comprehensive, and up-to-date analysis of the phytochemical composition of medicinal teas produced from native plant species of the Brazilian Cerrado, with emphasis on structural identification, chromatographic characterization, and bioactivity correlation of the major metabolites.

To this end, four species of high phytochemical relevance were selected based on criteria such as metabolic diversity, structural originality, use of modern structural elucidation methods, and previously described therapeutic potential: *Dipteryx alata* Vogel (baru), *Hancornia speciosa* Gomes (mangaba), *Bowdichia virgilioides* Kunth (sucupira-preta), and *Eugenia dysenterica* DC. (cagaita).

These species were chosen not only for the abundance and diversity of their secondary metabolites but also for the robustness and consistency of available phytochemical studies, which enabled the detailed identification of glycosylated flavonoids, condensed and hydrolyzable tannins, chalcones, iso-flavones, phenolic acids, and triterpenes using techniques such as NMR and high-resolution mass spectrometry.

The following sections will individually address the chemical profile of each plant, the extraction methods employed, the main isolated compounds, the correlations between chemical structure and biological function, and the proposed biosynthetic pathways. By compiling this evidence from a chemical perspective, this review aims to provide a solid scientific foundation for future research focused on the phytochemical, biotechnological, and pharmaceutical exploitation of native Cerrado species, while promoting their sustainable valorization and conservation.

Methods of literature search and inclusion criteria

To ensure the comprehensiveness and scientific rigor of this review, a systematic literature search was conducted between January and March 2025 using the

Scopus, ScienceDirect, and PubMed databases. The search strategy aimed to identify experimental studies characterizing the phytochemical composition of medicinal teas (infusions or decoctions) prepared from plant species native to the Brazilian Cerrado biome.

Boolean operators were used to combine relevant keywords, including the terms: “infusion” OR “decoction” AND “phytochemical composition” OR “bioactive compounds” OR “metabolites” AND [species name] AND “HPLC” OR “GC–MS” OR “LC–MS/MS” OR “NMR” OR “phytochemical analysis.” The search was limited to peer-reviewed articles published in English, Portuguese, or Spanish.

Strict inclusion criteria were adopted, prioritizing studies that: (a) provided experimental identification of phytochemical constituents in aqueous infusions or decoctions prepared using traditional or optimized methods; (b) employed advanced analytical techniques such as high-performance liquid chromatography (HPLC), gas chromatography–mass spectrometry (GC–MS), liquid chromatography–tandem mass spectrometry (LC–MS/MS), and one- and two-dimensional nuclear magnetic resonance spectroscopy (^1H , ^{13}C NMR, HSQC, HMBC); (c) included unambiguous botanical identification of the plant species studied; and (d) reported full or partial structural elucidation, or at least chemical classification of the compounds (e.g., flavonoids, tannins, alkaloids).

Based on these criteria, four species were selected due to their phytochemical relevance and the robustness of the available literature: *Dipteryx alata* Vogel (baru), *Hancornia speciosa* Gomes (mangaba), *Bowdichia virgilioides* Kunth (sucupira-preta), and *Eugenia dysenterica* DC. (cagaita). These species were prioritized for their high metabolic diversity and the consistent application of advanced analytical techniques, enabling detailed chemical elucidation of their bioactive constituents in aqueous preparations.

Dipteryx alata

Dipteryx alata, commonly known as baru, cumbaru, or cumaruzeiro, is a large leguminous tree belonging to the family Fabaceae, subfamily Papilionoideae (Antunes et al. 2020). It is a native and endemic species of the Brazilian Cerrado, widely distributed across the states of Goiás, Mato Grosso, Mato Grosso

do Sul, Minas Gerais, and São Paulo, reaching up to 25 m in height (Martinez and Teodoro 2024). Beyond its ecological relevance, *D. alata* holds significant socioeconomic and cultural importance. The baru nut is widely consumed as a food source and is considered rich in lipids, proteins, fiber, and bioactive compounds (de Miranda Monteiro et al. 2022).

Leaves, bark, and fruit pulp are traditionally used in folk medicine for the preparation of teas and infusions indicated for the treatment of muscular and joint pain, including rheumatism, lumbago, and osteoporosis; gynecological conditions such as prolonged menstruation, uterine inflammation, and vaginal discharge; renal and urinary disorders, with diuretic and analgesic effects; and gastrointestinal ailments such as gastritis, ulcers, and intestinal infections, among other therapeutic uses (Esteves-Pedro et al. 2012; Ribeiro et al. 2017).

Figure 1 illustrates the chemical structures of the five major compounds identified in the leaves, bark, pulp, and seeds of the species, with an emphasis on flavonoids and phenolic acids, which have been extensively studied for their antioxidant, anti-inflammatory, and wound-healing properties.

Table 1 summarizes the main studies on *D. alata*, highlighting the plant parts used, extraction methods, analytical techniques, identified compounds, pharmacological activities, and experimental models.

Importantly, most studies summarized in Table 1 did not directly reproduce traditional medicinal infusions or decoctions. Instead, they employed hydroalcoholic, methanolic, ethanolic, alkaline, ultrasound-assisted, oil-based, or chromatographically fractionated preparations. Therefore, these studies should be interpreted as complementary phytochemical and pharmacological evidence rather than direct validation of traditional aqueous preparations. This distinction is essential because extraction solvent, temperature, polarity, and processing conditions strongly influence metabolite recovery, structural stability, bioaccessibility, and biological activity, which may result in substantial differences between experimentally obtained extracts and traditional medicinal preparations used in folk medicine.

The reviewed literature reveals that *D. alata* is a remarkable source of chemical diversity, with bioactive compounds distributed distinctively across bark, leaves, pulp, almonds, and seeds. Extracts obtained from the trunk bark have shown prominent antiaphidic

effects against *Bothrops jararacussu* venom, primarily attributed to tannins, phenolic acids, and flavonoids such as quercetin, identified by thin-layer chromatography (TLC). These compounds are associated with the precipitation of toxic proteins and the formation of inactive complexes with phospholipase A2 enzymes (Nazato et al. 2010).

These findings were corroborated by Puebla et al. 2010, who isolated and structurally characterized a range of compounds—such as isoflavonoids, chalcones, and triterpenes—using advanced techniques including NMR and HRMS. The application of one- and two-dimensional NMR spectroscopy (¹H, ¹³C, HSQC, and HMBC) enabled the precise elucidation of complex structures, including glycosylated flavonoids.

The use of LC–MS/MS and UHPLC-DAD further contributed to the differentiation of structural isomers with minor variations in sugar chains or methoxylation positions, underscoring the importance of these techniques for analyzing plant matrices with high phytochemical complexity (Puebla et al. 2010; Ferraz et al. 2014; Nunes et al. 2024). Among the isolated compounds, 7,8,3'-trihydroxy-4'-methoxyisoflavone demonstrated high efficacy in neutralizing the neuromuscular and myotoxic effects induced by *Bothrops jararacussu* venom and its major myotoxin, bothropstoxin-I (BthTX-I), preventing up to 84% of neuromuscular blockade in mouse phrenic nerve–diaphragm preparations (Ferraz et al. 2014). This activity is related to the presence of phenolic hydroxyl groups at positions C-7, C-8, and C-3' of the isoflavone, whose configuration allows specific interactions with phospholipase A₂ enzymes in the venom, leading to the formation of reactive quinones that inactivate toxic proteins (Ferraz et al. 2014). This chemical structure underpins the compound's high potential for muscle membrane stabilization and prevention of venom-induced myonecrosis.

In addition to antiophidic effects, compounds found in the leaves and pulp have exhibited strong antioxidant activity. Methanol/water extracts and aqueous homogenates from the fruit pulp demonstrated high levels of total phenolics and flavonoids, with protective effects against oxidative stress in *Caenorhabditis elegans* in vivo models, promoting increased lifespan and activation of endogenous antioxidant pathways, such as DAF-16 nuclear translocation and upregulation of SOD-3 expression (Leite et al. 2020).

The use of alkaline solvents and hydroethanolic mixtures has proven effective for extracting these compounds, with 5% NaOH solution being particularly efficient in recovering phenolics and condensed tannins (da Silva et al. 2021). Baru almonds have also emerged as promising sources of bioactive compounds. Ethanolic extracts have shown high concentrations of gallic acid and significant antioxidant and wound-healing activities, promoting epithelial regeneration in pulmonary cell lines (Coco et al. 2022).

Another noteworthy finding is the selective cytotoxicity exhibited by pulp-with-peel extracts against tumor cell lines (SiHa and C33A), with minimal effects on non-tumorigenic cells (HaCaT, L929), indicating potential applications in preventive or therapeutic oncology (Barizão et al. 2021). The phenolic composition of this fraction—rich in trans-cinnamic acid, protocatechuic acid, luteolin, and naringenin—supports the hypothesis of synergistic interactions among metabolites in the induction of apoptosis and inhibition of tumor cell proliferation.

The formulation of nanoemulsions from baru almond oil has demonstrated promising physicochemical stability and functional potential for food, cosmetic, and pharmaceutical applications, particularly due to the interfacial behavior of crude baru oil and the antioxidant properties associated with phenolic compounds and tocopherols (de Oliveira Paulo et al. 2023; Queiroz et al. 2025). Recent spectrometric analyses revealed even greater phytochemical diversity, with the tentative identification of numerous compounds by PS–MS, including flavonoids, gallotannins, phenolic acids, chalcones, glycosides, triterpenes, and organic acids distributed across peel, pulp, endocarp, raw almond, and roasted almond fractions (Nunes et al. 2024).

The leaves, in turn, contain novel glycosylated flavonoids such as quercetin-3-O- β -glucoside-7-O- α -rhamnoside and quercetin-7-O- α -rhamnoside, which have shown strong anti-inflammatory and antioxidant activities in in vivo models of pain, edema, and nitric oxide production (Dos Santos et al. 2025).

Additionally, thermal processing of the almonds was found to directly influence their phytochemical profile. Compounds such as quercetin, gallic acid derivatives, tannins, and other phenolic metabolites were detected in raw and roasted almond fractions, suggesting that thermal processing may alter metabolite availability, promote the release of matrix-bound

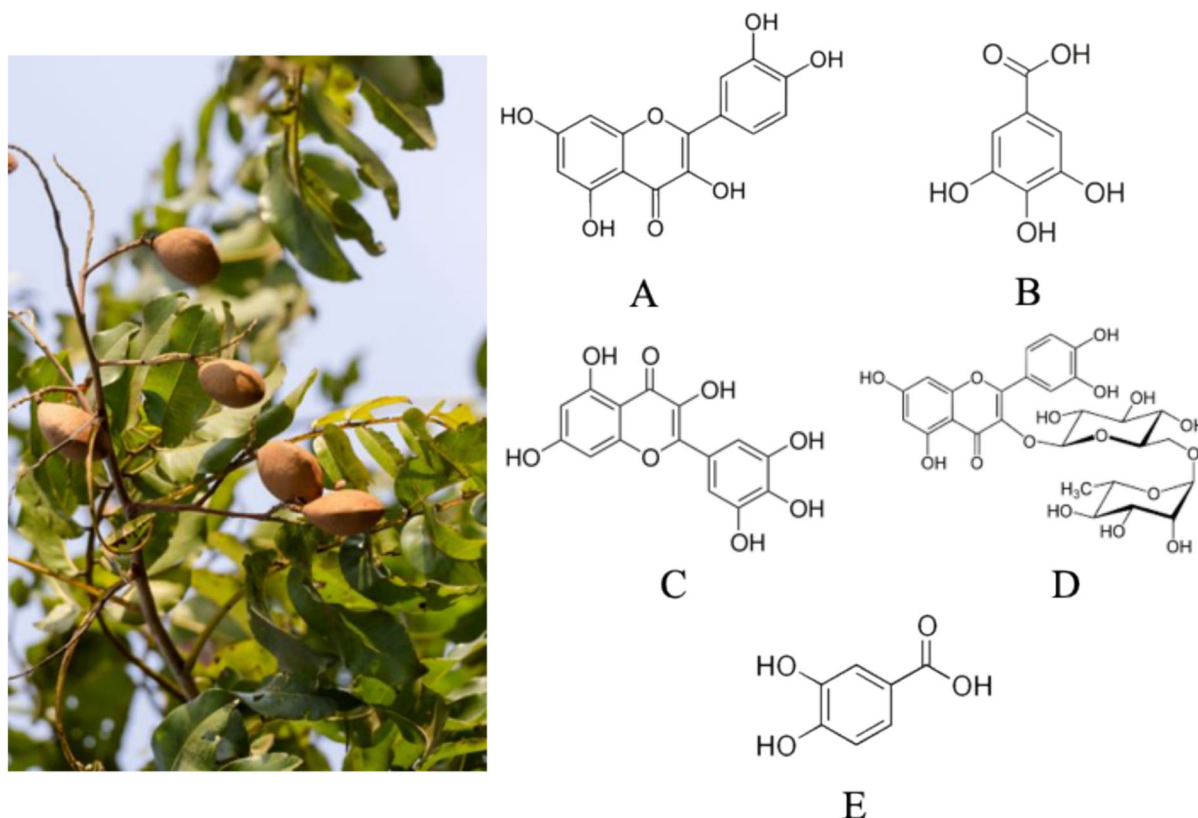


Fig. 1 *Dipteryx alata* tree and its main bioactive compounds identified in different parts of the plant: **A** quercetin, **B** luteolin, **C** rutin, **D** gallic acid and **E** protocatechuic acid

compounds, or contribute to the formation of processing-derived derivatives (Nunes et al. 2024). This evidence underscores the importance of post-harvest processing in modulating the bioactivity of *D. alata* derivatives.

The recurrent detection of flavonoids and phenolic acids such as luteolin, quercetin, and gallic acid in various plant parts highlights the systematically bioactive nature of *D. alata*, which exhibits a broad pharmacological spectrum. These compounds mainly belong to the classes of flavonols, phenolic acids, and isoflavonoids, all known for their high antioxidant activity and ability to interact with biological targets such as oxidative enzymes, inflammatory mediators, and toxic proteins (Al-Khayri et al. 2022; Chagas et al. 2022).

In particular, the polyhydroxylated structure of these compounds enhances their ability to act as free radical scavengers, anti-inflammatory agents, and stabilizers of cellular membranes (Murias et al.

2005; Nájera-Maldonado et al. 2024). The recurrent presence of these bioactive compounds in different plant fractions reinforces the potential of *D. alata* as a versatile source for the development of functional extracts with broad therapeutic applications.

In terms of safety, the reviewed studies generally reported low toxicity for several evaluated extracts, including cell-based assays, *Artemia salina*, *Allium cepa*, *C. elegans*, keratinocytes, erythrocytes, and in silico toxicity predictions. However, comprehensive in vivo, chronic toxicity, and clinical safety assessments remain scarce, limiting definitive conclusions regarding long-term therapeutic use (Nazato et al. 2010; Leite et al. 2020; Lima et al. 2022; Scapin et al. 2024; Queiroz et al. 2025; Dos Santos et al. 2025). These findings support the therapeutic potential of *D. alata* for both topical and systemic use, in natural or nano-structured formulations, with possible applications in phytotherapy, dentistry, functional foods, and cosmetics.

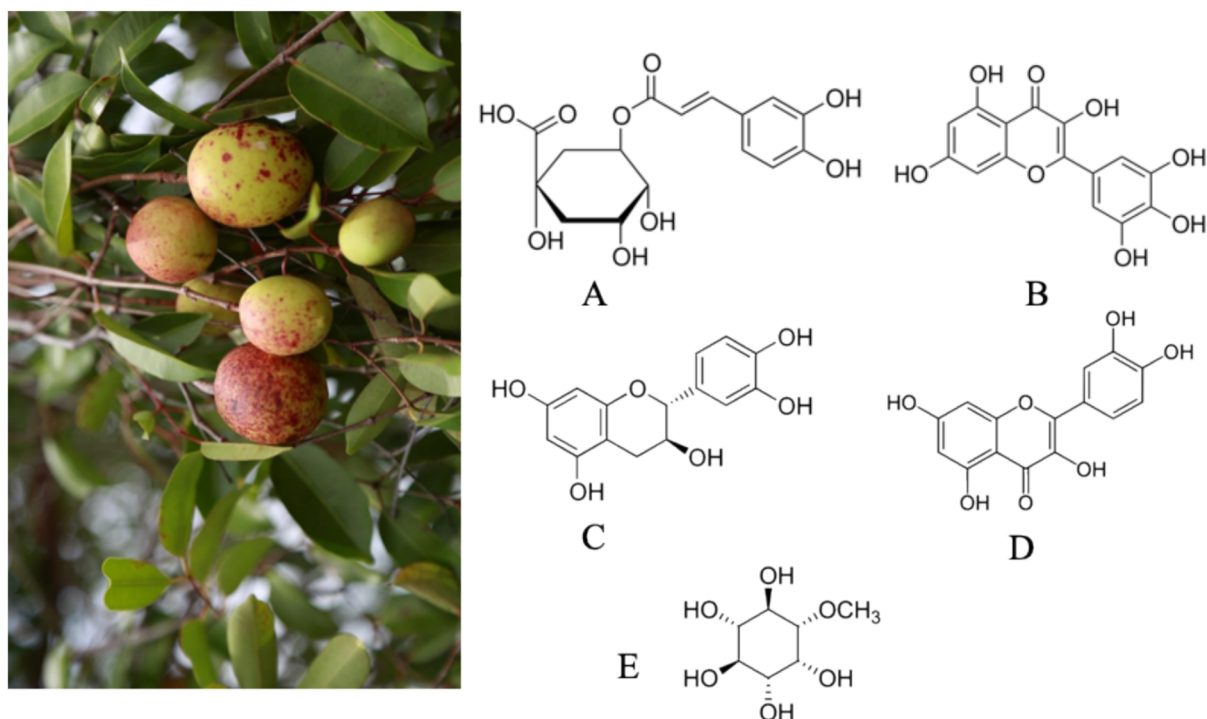


Fig. 2 Main bioactive compounds identified in *Hancornia speciosa*: **A** chlorogenic acid, **B** rutin, **C** catechin, **D** quercetin and **E** bornesitol

Structure–activity relationship (SAR) analysis of the compounds identified in *D. alata* reveals structural patterns that largely explain their biological activities. Flavonoids such as quercetin, luteolin, and rutin possess a flavonol backbone with multiple hydroxyl groups on rings A and B, which confer high antioxidant potential through electron donation and free radical stabilization (Cos et al. 2000; Singh et al. 2021). Specifically, hydroxyl groups at positions C-3' and C-4' on ring B, and C-5 and C-7 on ring A, promote metal chelation and the inhibition of pro-oxidant enzymes such as NADPH oxidase and xanthine oxidase (Luo et al. 2022; Abou Baker 2022). Rutin, with rhamnose and glucose moieties attached at position C-3, exhibits increased water solubility, improving its bioavailability in infusions and enhancing its stability in phytotherapeutic preparations (Kapešová et al. 2019; Křen & Bojarová, 2023).

Regarding phenolic acids such as gallic acid, protocatechuic acid, and caffeic acid, the presence of carboxyl groups conjugated to polyhydroxylated

aromatic systems contributes to lipid peroxidation inhibition and modulation of inflammatory pathways, including NF- κ B signaling (Mucha et al. 2021; Rathod et al. 2023). These compounds function as reactive oxygen species (ROS) scavengers and inhibitors of enzymes such as COX-2 and LOX, primarily through hydrogen bonding and hydrophobic interactions with catalytic sites (Molehin et al. 2023; Rudrapal et al. 2024).

Triterpenic compounds such as lupeol and betulin, identified in the bark and almonds, possess a pentacyclic core with a hydroxyl group at the C-3 position, which enables their action in modulating inflammatory responses, particularly through the inhibition of mediators such as TNF- α and IL-1 β (Renda et al. 2022). The rigid and hydrophobic structure of these compounds favors interactions with nuclear receptors (e.g., PPAR γ) and cellular membrane components, supporting their effectiveness in models of pain and chronic inflammation (Sharma and Lee 2021; Enayati et al. 2022; Spanoudaki et al. 2024).

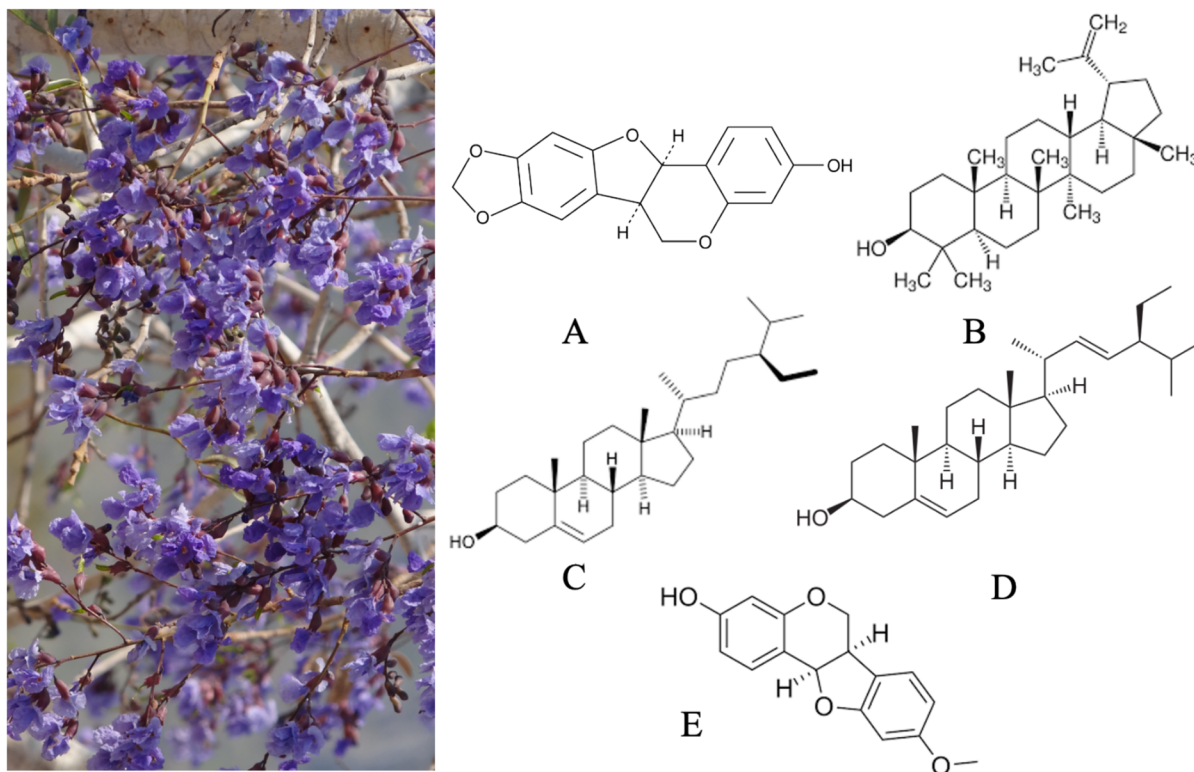


Fig. 3 *B. virgilioides* and chemical structures of representative structurally characterized compounds: **A** Maackiain, **B** Lupeol, **C** β -Sitosterol, **D** Stigmasterol and **E** Medicarpin

Although the phytochemical findings for *D. alata* highlight promising compounds, the lack of clinical trials and in vivo validations for many extracts and fractions limits the therapeutic consolidation of this species. Most studies remain confined to in vitro models, with a scarcity of systematic in vivo assessments and a complete absence of controlled clinical trials. Furthermore, few compounds have been evaluated in isolation and in a systematic manner, making it difficult to distinguish intrinsic effects from potential synergistic interactions among the metabolites present in crude extracts.

Another recurring challenge is the lack of standardized protocols for extraction, fractionation, and quantification, which compromises comparability across studies and hinders progress toward technological development. Although the *D. alata* almond is widely studied and commercially valued, other parts of the plant—such as the bark, leaves, and pulp—contain significant concentrations of bioactive compounds but remain underexplored from a

phytochemical and functional perspective, representing an untapped potential for the integral utilization of the species.

It is worth noting that more than fifty metabolites recently identified by PS–MS in bark, pulp, and almond extracts of *D. alata* have yet to undergo functional studies or detailed structural investigations (Nunes et al. 2024). The absence of data on their biosynthetic pathways, chemical stability, and mechanisms of action limits their application, yet also presents a significant opportunity for the discovery of new bioactive candidates with pharmaceutical and nutraceutical potential.

In this context, further advancement in the phytochemical and bioactive knowledge of *D. alata* should involve integrated approaches, including untargeted metabolomics, bioassay-guided fractionation, mechanistic studies, and stability analysis in complex formulations. Such advances will be crucial to support the rational and scientific use of this species, accelerating its inclusion in innovative production chains and

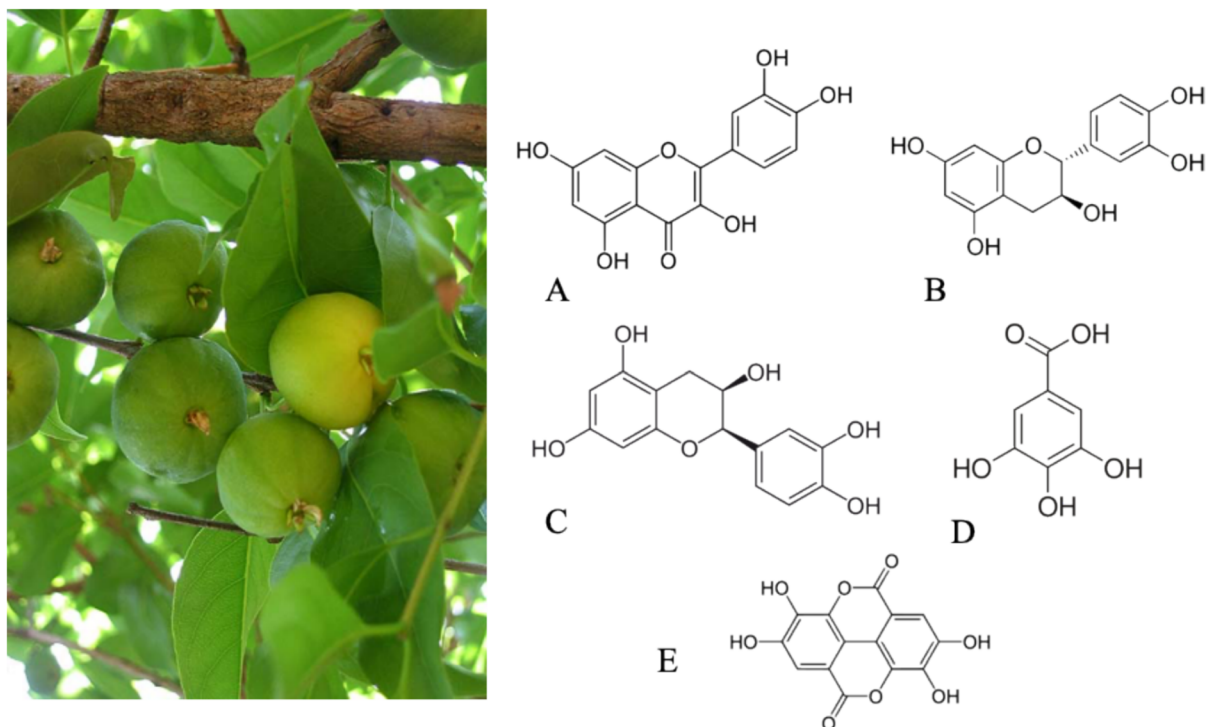


Fig. 4 *Eugenia dysenterica* and representative bioactive compounds identified across different plant parts and preparation/extraction systems

promoting the biotechnological valorization of the Brazilian Cerrado as a strategic reservoir of natural resources.

Hancornia speciosa

Hancornia speciosa, commonly known as “manga-beira”, is a plant native to Brazil and belongs to the Apocynaceae family. It is widely distributed across several Brazilian biomes, including the Caatinga, Amazon, Cerrado, and Atlantic Forest, and is also found in neighboring countries such as Bolivia, Peru, and Paraguay (Vieira et al. 2016). Its fruits, known as mangabas, have significant socioeconomic importance. They are consumed fresh or processed by small-scale agro-industries into juices, ice creams, sweets, and jams, serving as a crucial source of income for traditional communities, especially the traditional catadoras de mangaba (mangaba gatherers) (Soares et al. 2011; Almeida et al. 2022; Nunes et al. 2022).

Figure 2 presents representative bioactive compounds reported in studies of *H. speciosa*: (A) chlorogenic acid, (B) rutin, (C) catechin, (D) quercetin, and (E) bornesitol.

Table 2 summarizes the main phytochemical and pharmacological information extracted from recent studies on different parts of *H. speciosa*, highlighting the identified compounds, analytical methods used, observed biological activities, proposed mechanisms of action, and research gaps.

Importantly, several studies summarized in Table 2 did not directly reproduce traditional medicinal infusions or decoctions commonly employed in folk medicine. Instead, many investigations used hydroethanolic, ethanolic, methanolic, acetone/water, pressurized, fractionated, chromatographically purified, latex-derived, or in vitro cell culture-based preparations to improve metabolite recovery and structural characterization. Therefore, these studies should be interpreted as complementary phytochemical and pharmacological evidence rather than direct validation of traditional aqueous preparations. This

Table 1 Comparison of phytochemical and pharmacological studies involving *Dipteryx alata* Vogel and its different preparation/extraction systems

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Stem bark	Sequential Soxhlet extraction with hexane, dichloromethane, ethyl acetate and methanol; hydroalcoholic extraction with 70% ethanol	Caffeic acid, chlorogenic acid, tannic acid, rutin, quercetin, apigenin, tannins, flavonoids and terpenoids	TLC, spectrophotometric tannin quantification and phytochemical screening	In vitro antipthidian activity against <i>Bothrops</i> <i>jararacussu</i> and <i>Crotalus durissus</i> <i>terrificus</i> venoms; reduction of neurotoxicity and myotoxicity	Tannins likely precipitate venom proteins; phenolic compounds and flavonoids may inhibit phospholipases and other venom enzymes	No direct toxicity evaluation; methanolic extract caused minimal muscle fiber alterations in isolated preparations	Exclusively in vitro assays; active compounds not isolated individually; mechanisms remain partially speculative	Nazato et al. (2010)
Stem bark	Hydroalcoholic extraction followed by partition with hexane, dichloromethane, ethyl acetate and methanol; silica gel and Sephadex LH-20 chromatographic fractionation	Lupicol, lupenone, betulin, 28-hydroxylup- 20(29)-en-3-one, afromosin, odoratin, dipteryxin, 8-O- methylretusin, isoliquritigenin, sulfuretin, vanillic acid, vanillin and protocatechuic acid	GC-MS, HR-ESI- MS, IR spectroscopy, 1D/ 2D-NMR, TLC and chromatographic fractionation	In vitro inhibition of neuromuscular blockade and myotoxicity induced by <i>Bothrops</i> <i>jararacussu</i> venom	Isoflavonoids and phenolic acids likely interact with venom phospholipases and neurotoxins, attenuating toxic effects	No direct toxicity or cytotoxicity assays performed	Exclusively in vitro study; isolated compounds were not individually pharmacologically evaluated	Puebla et al. (2010)
Fruit pulp and almonds/ seeds	Ultrasound-assisted extraction, Soxhlet extraction and Bligh & Dyer lipid extraction	Tannins, oleic acid, linoleic acid, linolenic acid and saturated fatty acids	GC-MS and spectrophotometric assays	Nutritional and functional potential associated with antioxidant compounds and lipid profile	Ultrasound-assisted extraction improved tannin recovery and preservation of unsaturated fatty acids	No toxicity or safety assays performed	No biological assays confirming pharmacological activity; focus restricted to extraction optimization and chemical characterization	Martins et al. (2013)
Stem bark	Hydroalcoholic extraction with 70% ethanol, liquid-liquid partition and chromatographic purification	7,8,3'-Trihydroxy-4'- methoxyisoflavone (TM)	IR spectroscopy, 1H- NMR, 13C-NMR and chromatographic techniques	In vitro inhibition of neuromuscular paralysis and myonecrosis induced by <i>Bothrops</i> <i>jararacussu</i> venom and bothropstoxin-I	Hydroxyl groups of TM likely generate reactive quinone intermediates capable of interacting with phospholipases and venom enzymes	No mutagenicity observed in Ames test using <i>Salmonella</i> <i>typhimurium</i> TA97a and TA98 strains	Exclusively in vitro study; low yield of purified compound limited additional pharmacological analyses	Ferraz et al. (2014)

Table 1 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Almonds/ seeds	Preparation of water- soluble extract by grinding with water, centrifugation, pasteurization and refrigerated storage	Phenolic compounds and antioxidant compounds	Spectrophotometric assays for total phenolics and antioxidant activity	Antioxidant potential and possible application as plant- based functional beverage	Antioxidant activity associated with phenolic compounds present in the hydrosoluble extract	No toxicity or safety assays performed	Individual compounds were not structurally identified; absence of biological and clinical assays	da Silva et al. (2020)
Fruit pulp	Methanol/water extraction (0.1% formic acid) combined with aqueous homogenization for in vivo assays	Luteolin, O-hexosyl protocatechuic acid, di-O-methoxy dihydroxy isoflavone, citric acid, ascorbic acid, lycopene, chlorophyll a, chlorophyll b, phenolic acids, flavonoids, terpenes and fatty acid derivatives	LC-DAD-MS/MS, spectrophotometric assays, DPPH and ABTS radical scavenging assays	In vitro and in vivo antioxidant activity; increased oxidative stress resistance and lifespan in <i>Caenorhabditis elegans</i>	Antioxidant effects associated with ROS scavenging, increased SOD-3 expression and DAF-16 nuclear translocation	No toxicity observed in <i>C. elegans</i> ; no alterations in viability or reproductive capacity	Restricted to <i>C. elegans</i> and in vitro assays; several compounds were putatively identified rather than fully isolated	Leite et al. (2020)
Fruit pulp and peel/ bark	Dehydrated pulp flour extracted with acetone, ethanol, water, acetic acid, NaOH, Na ₂ CO ₃ and sodium sulfite mixtures under orbital shaking followed by centrifugation	Phenolic compounds, flavonoids, condensed tannins, catechin, phenolic acids, coumarins, stilbenes, lignans and lignin-derived compounds	Folin-Ciocalteu assay, aluminum chloride colorimetric assay, vanillin-HCl assay and atomic absorption spectrophotometry	Antioxidant and nutritional potential; possible industrial application as antioxidant source and substitute for synthetic phenols in adhesives, cosmetics and food products	Phenolic compounds and tannins may act through free radical scavenging and oxidative stress reduction; alkaline and sulfite solutions increased tannin solubility by opening heterocyclic flavan-3-ol structures	No direct toxicity assays performed; authors discuss possible antinutritional effects of tannins due to reduced mineral and protein bioavailability and increased bitterness	No in vitro or in vivo pharmacological validation; individual compounds were not isolated or structurally elucidated; focus centered on extraction efficiency and nutritional characterization	da Silva et al. (2021)
Nuts/seeds	Ethanol extraction of baru nuts (BNEE)	Gallic acid and total phenolic compounds	HPLC, total phenolic quantification and DPPH assay	Antioxidant activity and wound healing activity in NCI- H441 and A549 lung epithelial cell lines	Reduction of reactive oxygen species (ROS) during oxidative stress and enhancement of epithelial wound closure	No cytotoxicity observed at tested concentrations	In vitro study restricted to lung epithelial cell lines; no in vivo or clinical validation; molecular mechanisms not fully elucidated	Coco et al. (2022)

Table 1 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Pulp + peel	Ultrasound-assisted extraction (UAE) using ultrapure water, absolute methanol, absolute ethanol, aqueous methanol (80%) and aqueous ethanol (80%); hydroethanolic extracts prepared from lyophilized pulp + peel powder	Luteolin, trans- cinnamic acid, protocatechuic acid, gallic acid, chlorogenic acid, vanillic acid, (-)- epicatechin, caffeic acid, syringic acid, p-coumaric acid, sinapic acid, ferulic acid, rutin, myricetin, quercetin, naringenin and apigenin	UHPLC-MS/MS, DPPH assay, ORAC assay and Folin–Ciocalteu assay	Antioxidant activity and selective in vitro cytotoxic activity against cervical cancer cell lines (SIHa and C33A)	Antioxidant activity associated with phenolic compounds; cytotoxic activity possibly related to luteolin, trans-cinnamic acid and protocatechuic acid, which may contribute to oxidative stress modulation and cancer cell viability reduction	Weak cytotoxicity against non-tumor HaCaT and L929 cell lines, suggesting relative safety at tested concentrations	Exclusively in vitro study; no in vivo or clinical validation; synergistic effects among compounds were suggested but not experimentally confirmed	Barizão et al. (2021)
Seed oil	Cold-pressed crude oil used for preparation of oil-in-water (O/W) nanoemulsions stabilized with Tween 80 under different pH and NaCl conditions	Oleic acid, linoleic acid, linolenic acid, palmitic acid, stearic acid, phenolic compounds, carotenoids, terpenes, tocopherols and phytosterols	Rheological analysis, pendant drop tensiometry, zeta potential analysis, dynamic light scattering (DLS), optical microscopy and physicochemical characterization	Potential application in food, cosmetic and pharmaceutical nanoemulsions with kinetic stability and functional properties	Surfactant molecules and bioactive compounds present in crude baru oil contributed to interfacial stabilization, electrostatic repulsion and elastic interfacial behavior, delaying droplet coalescence and phase separation	Nanoemulsions showed relative kinetic stability for up to 28 days without macroscopic phase separation under most tested conditions	Study focused on physicochemical and interfacial properties; no biological, toxicological or in vivo evaluation of nanoemulsions	de Oliveira Paulo et al. (2023)
Leaves	Ultrasound-assisted extraction with 70% ethanol (UCE); Soxhlet extraction with 70% ethanol (SCE); Soxhlet extraction after hexane degreasing followed by 70% ethanol extraction (SEE)	Gallic acid, caffeic acid, rutin, quercetin, luteolin, kaempferol, campesterol, β - sitosterol, flavonoids, tannins, phytosterols, saponins and alkaloids	LC-DAD, GC-MS, phytochemical screening, Folin– Ciocalteu assay, DPPH• assay and ABTS• + assay	Antioxidant activity; antibacterial activity against <i>Staphylococcus aureus</i> and <i>Streptococcus mutans</i> ; potential therapeutic applicability in oral health and dentistry	Phenolic compounds and flavonoids may promote free radical scavenging; tannins may interfere with bacterial adhesion and biofilm formation; quercetin may reduce pro-inflammatory cytokines and stimulate epithelial homeostasis; kaempferol may disrupt Gram-positive bacterial cell wall and membrane integrity	Low toxicity in <i>Artemia salina</i> assay; root growth stimulation in <i>Allium cepa</i> at lower concentrations; SEE inhibited root growth at 750 µg/mL; no antifungal activity against <i>Candida albicans</i>	No in vivo or clinical studies; mechanisms mainly inferred from literature correlations; antifungal activity was not confirmed experimentally	Scapin et al. (2024)

Table 1 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Peel, pulp, endocarp, raw almonds and roasted almonds	Methanolic extraction of fresh homogenized plant material followed by paper spray ionization	Citric acid, ellagic acid, protocatechuic acid hexoside, isofenolic acid, luteolin, vicenin-2, trigalloylglucose, tetragalloylglucose, pentagalloylglucose, eucomic acid, pinocembrin, p-coumaroyl-malic acid, eriodictyol, feruloyl-malic acid, vanillin hexoside, myricetin, coumaroyl hexose, caffeic acid- O-hexoside, ferulic acid hexoside, syringic acid hexoside, isovitexin, eriodictyol-O- glucoside, quercetin- 3-O-glucuronide, dihydromyricetin glucoside, noricartin hexoside, phloretin glycosides, isorhamnetin glycosides, procyanidin trimer, calycosin, stigmastanol, tricafeoylquinic acid, sutherlandin, ellagic acid derivatives, mangiferin derivatives, astragaloside I, chalcones, flavonoids, tannins, phenylpropanoids, benzoic acid derivatives and organic acids	Paper spray mass spectrometry (PS- MS) in positive and negative ionization modes with MS/MS fragmentation analysis	Potential antioxidant, anti-inflammatory, antitumoral, antiproliferative, antidiabetic, cardioprotective and antimicrobial activities inferred from the identified phytochemicals	Biological activities were associated mainly with flavonoids, gallotannins and phenolic compounds that may contribute to free radical scavenging, anti-inflammatory responses, inhibition of tumor cell proliferation and modulation of oxidative stress	No experimental toxicity or safety assays were performed in this study	Compounds were tentatively identified rather than fully isolated; no in vitro or in vivo biological assays were conducted; pharmacological effects were inferred from literature reports on identified compounds	Nunes et al. (2024)

Table 1 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Nut oil	Cold-pressed oil nanoemulsion (BNON) prepared by spontaneous emulsification using lecithin and poly sorbate 80; ultrasonic homogenization	Oleic acid, linoleic acid, α -tocopherol and phenolic compounds	DPPH assay, dynamic light scattering (DLS), zeta potential analysis, atomic force microscopy (AFM), MTT assay and hemolysis assay	Antioxidant activity; protection against AAPH-induced oxidative stress in erythrocytes; potential application in health and cosmetic nanobiotechnology	Antioxidant activity associated with free radical scavenging and hydrogen donation mechanisms mediated by phenolic compounds and tocopherols; nanoemulsion components contributed to nanodroplet stabilization and delivery	Free oil showed no cytotoxicity toward human keratinocytes or erythrocytes at tested concentrations; nanoemulsion showed cytotoxicity only at highest concentrations and mild erythrocyte morphological alterations	Nanoemulsion requires further optimization due to precipitation and increased polydispersity; antioxidant protection was weaker in nanoemulsion than in free oil; no in vivo or clinical evaluation	Queiroz et al. (2025)
Leaves	Lyophilized leaf infusion (LI-DA) prepared with distilled water at 80 °C for 15 min; liquid–liquid partition yielding ethyl acetate fraction (EAF-DA) and hydromethanolic fraction (HMF-DA); chromatographic isolation of flavonoids	Quercetin-3-O- β - glucoside-7-O- α - rhamnoside (DA-1), quercetin-7-O- α - rhamnoside (DA-2), quercetin glycosides and flavonol glycosides	NMR spectroscopy (¹ H, ¹³ C, COSY, HSQC and HMBC), TLC, Sephadex LH-20 chromatography, DPPH, ABTS, H2O2 scavenging, β -carotene bleaching and reducing power assays	Antioxidant, anti- inflammatory, anti- arthritic and antinociceptive activities; reduction of edema, leukocyte migration, nitric oxide production, mechanical and cold allodynia in CFA- induced inflammation models	Antioxidant activity associated with radical scavenging and inhibition of oxidative stress; DA-1 and DA-2 may modulate inflammatory cytokines, inhibit neutrophil/macrophage recruitment, reduce MPO and NAG activity, inhibit NO production and interact with PPAR- γ signaling pathways	In silico prediction indicated low hepatotoxicity, mutagenicity and cytotoxicity for DA- 1 and DA-2; both compounds showed predicted nephrotoxicity and DA-2 showed predicted carcinogenicity; no in vivo toxicity assay performed	Limited by small amounts of isolated compounds; no clinical validation; mechanisms not fully elucidated; toxicity assessment restricted to in silico analysis	Dos Santos et al. (2025)

Table 2 Comparison of phytochemical and pharmacological studies involving *Hancornia speciosa* Gomes and its different preparation/extraction systems

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Latex	Latex stabilized with distilled water or ammonia; biomembrane polymerization	cis-1,4-polyisoprene	FTIR, TGA, CHN analysis, comet assay	Angiogenic and biomaterial potential	Neovascularization and inflammatory-cell- mediated remodeling	Water-eluted latex showed no cytotoxicity or genotoxicity; ammonia-stabilized latex reduced cell viability	No phytochemical profiling of secondary metabolites; no mammalian in vivo validation	Almeida et al. (2014)
Latex	Aqueous latex phase incorporated into carbol gel	Chlorogenic acid, naringenin-7-O- glucoside, catechin, procyanidins	ESI-MS/MS, Folin-Ciocalteu, MTT	Osteogenic and bone regenerative activity	Stimulation of osteoblast proliferation and bone formation	Non-cytotoxic below 0.3 mg/mL	No isolation of active compounds; absence of clinical studies	Dos Santos Neves et al. (2016)
Fruits	Aqueous decoction followed by lyophilization	Chlorogenic acid, rutin, unidentified phenolic acid	HPLC-DAD, LC- MS	Anti-inflammatory activity	NF- κ B suppression and reduction of inflammatory mediators and leukocyte migration	No significant toxicity in 3T3 cells; no inflammatory response induced in vivo	Mechanisms not fully elucidated; unidentified phenolic constituents	Torres-Rêgo et al. (2016)
Leaves	Hydroethanolic maceration followed by C18 cleanup	Procyanidins, catechin, epicatechin, chlorogenic acid, rutin, quercetin derivatives, luteolin, apigenin, kaempferol	UHPLC Orbitrap- HRMS/MS	Potential antihypertensive, antidiabetic and antioxidant activities	ACE inhibition, vasodilation, α - glucosidase inhibition and NF- κ B modulation inferred from literature	No experimental toxicity assays performed	Activities inferred from phytochemical composition; several compounds putatively identified	Bastos et al. (2017)
Leaves	Ethanolic maceration followed by freeze-drying	Rutin, catechin, isoquercetin, chlorogenic acid, quercetin, kaempferol, epicatechin, procyanidins, carotenoids	HPLC-DAD-MS/ MS, GC-FID, Ames test	Antioxidant, anti- inflammatory, antibesity, antihyperglycemic and neuroprotective activities	Radical scavenging, enzyme inhibition and inflammatory modulation	No relevant toxicological concerns; antimutagenic activity observed	No clinical validation; synergistic interactions not experimentally confirmed	Santos et al. (2018)
Fruits	Aqueous decoction followed by solvent partitioning	Rutin, chlorogenic acid, gallic acid, catechin, ferulic acid, rosmarinic acid	HPLC-DAD, LC- MS, ELISA	Anti-inflammatory, lung-protective and antivenom activity	Reduction of cytokines, nitric oxide, leukocyte recruitment, and inflammatory lung injury	No acute toxicity signs reported	No clinical validation; contribution of unidentified compounds unclear	Bitencourt et al. (2019)
Leaves	Sequential pressurized liquid extraction	Rutin, chlorogenic acid, kaempferol, flavonoids and phenolic compounds	HPLC-UV, Folin- Ciocalteu, DPPH assay	Antioxidant and antibacterial activities	Free radical scavenging and bacterial membrane disruption	No toxicity assays performed	Restricted to in vitro assays; no isolation of active compounds	Barbosa et al. (2019)
Cell suspension cultures derived from leaves/calli	In vitro culture under different carbon sources followed by methanolic extraction	Chlorogenic acid, epicatechin, rosmarinic acid, hesperidin, rutin, quercetin	HPLC-DAD	Potential antioxidant and biotechnological applications	Osmotic modulation of phenolic biosynthesis	Cell survival above 94% under all conditions	No pharmacological or in vivo assays performed	Dantas et al. (2021)

Table 2 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Leaves	Ethanol/water and methanol/ethyl acetate extraction; chromatographic isolation	Chlorogenic acid, rutin, bornesitol, quinic acid, lupeol ester derivatives, flavonoids	HPLC–PDA, UPLC–DAD– ESI–MS/MS, NMR	Antihypertensive and antidiabetic potential	Vasorelaxation, ACE inhibition and α - glucosidase inhibition	No direct toxicity evaluation	No in vivo confirmation of dual pharmacological effects	Pereira et al. (2022)
Fruit pulp	Hydroethanolic extraction followed by lyophilization	Phenolic compounds, vitamin C, carotenoids, reducing sugars	HPLC–PDA, DPPH, FRAP, TBARS	Antioxidant activity	Iron-reducing power and inhibition of lipid peroxidation	No toxicity assays performed	No identification of individual phenolics; absence of in vivo validation	Martins et al. (2023)
Leaves	Acetone/water extraction followed by Sephadex LH-20 fractionation	Bornesitol, chlorogenic acid, rutin, kaempferol, dimeric and trimeric B-type procyanidin C-glycosides	UPLC–DAD–ESI– MS/MS, thiolysis, ELISA, DCFH- DA assay	Anti-inflammatory, antioxidant and antihypertensive potential	Reduction of oxidative stress and TNF/IL-1 β release; NF- κ B modulation	No cytotoxicity or in vivo toxicity assays reported	Restricted to in vitro assays; no pharmacokinetic evaluation	Junior et al. (2024)
Latex	Crude latex fractionated into > 10 kDa and < 10 kDa fractions	Chlorogenic acid, galactose-rich carbohydrates, phenolic compounds	Folin–Ciocalteu, HPLC monosaccharide analysis, MTT, flow cytometry	Leishmanicidal activity	Arginase inhibition, oxidative stress modulation and cytokine regulation	Low cytotoxicity toward macrophages	Composition of < 10 kDa fraction not fully elucidated; no in vivo validation	Castro et al. (2024)
Stem bark	Sulfuric ether and methanolic extraction	Triterpenoids, phenolic acids, flavonoids, catechins, proanthocyanidins, tannins, phyosterols	GC–MS, Folin– Ciocalteu, microdilution assay	Antibiotic-modifying activity	Enhancement of antibiotic efficacy and membrane-related synergistic effects	Non-toxic in <i>Drosophila melanogaster</i>	No intrinsic antibacterial activity; mechanisms not fully elucidated	da Silva et al. (2024)

Table 3 Comparison of phytochemical and pharmacological studies involving *Bowdichia virgilioides* Kunth and its different preparation/extraction systems

Part used	Preparation/Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Stem inner bark and leaves	Aqueous extract prepared by infusion in boiling distilled water followed by lyophilization	Flavonoids, tannins, triterpenes and saponins	Phytochemical screening and DPPH assay	Antinociceptive, anti-inflammatory and antioxidant activities	Effects may involve inhibition of inflammatory mediators, COX/iNOS-related pathways and free radical scavenging	Low acute toxicity; LD50 > 5 g/kg for stem inner bark extract	No isolation or structural elucidation of individual compounds; mechanisms inferred from pharmacological models	Thomazzi et al. (2010)
Stem bark	Aqueous extract prepared by infusion of powdered stem bark followed by filtration, solvent evaporation and lyophilization	Alkaloids, flavonoids, triterpenoids and resinous constituents	Behavioral pharmacological assays; no direct phytochemical characterization performed	Anxiolytic-like activity after acute and sub-chronic oral treatment without locomotor impairment or myorelaxant effects	Effects may involve modulation of CNS-related pathways associated with flavonoids and triterpenoids	No mortality or motor coordination impairment observed at tested doses	No direct phytochemical characterization of the extract; mechanisms not experimentally elucidated; no receptor-binding or neurochemical assays	Vieira et al. (2013)
Stem inner bark	Hydroethanolic extraction followed by oral administration in resistance-trained rats	Medium- to high-polarity phenolic compounds and flavonoid-like constituents detected by HPLC-DAD fingerprinting	HPLC-DAD, DPPH assay, TBARS assay and total phenolic quantification	Antioxidant and protective effects against muscular damage and oxidative stress induced by high-intensity resistance training	Reduction of lipid peroxidation and oxidative stress through free radical scavenging and transition metal chelation	No evident toxicological alterations reported during treatment	Individual compounds were not structurally identified; mechanisms inferred mainly from antioxidant assays; study restricted to short-term animal model	Dos Santos et al. (2014)
Root bark	Sequential hexane and methanolic extraction by maceration followed by solvent evaporation	Alkaloids, flavonoid-like constituents and terpenoids detected by preliminary phytochemical characterization	Preliminary phytochemical screening and in vivo antihyperglycemic assays	Acute antihyperglycemic activity and improvement of oral glucose tolerance in diabetic rats	Possible modulation of intestinal glucose absorption and GLUT2-related pathways	No mortality observed up to 5000 mg/kg; transient somnolence at high doses	Individual compounds were not structurally identified; mechanisms remain speculative; no clinical validation	Silva et al. (2015)
Heartwood	Ethanolic extraction followed by cyclohexane partition and chromatographic fractionation	Maackiain, medicarpin, flavonoids, terpenoids, steroids and alkaloids	TLC, GC-MS, ¹ H/ ¹³ C NMR, HSQC and phytochemical screening	Larvicidal activity against <i>Aedes aegypti</i> larvae	Larvicidal effects mainly associated with the isoflavonoid maackiain	No toxicity evaluation in non-target organisms or mammalian systems	Mechanisms of larvicidal action were not elucidated; toxicity selectivity not investigated	Bezerra-Silva et al. (2015) et al. (2015)
Stem bark	Hydroethanolic extraction followed by liquid-liquid partitioning into hexane, chloroform, ethyl acetate and hydromethanolic fractions	Tannins, flavonoids, catechins, triterpenes, alkaloids, steroids and saponins	Phytochemical screening, Folin-Ciocalteu assay and DPPH radical scavenging assay	Antioxidant and antinociceptive activities in formalin-, glutamate- and capsaicin-induced orofacial pain models	Antinociceptive effects may involve opioid, glutamatergic and TRPV1-related pathways associated with ROS modulation	No impairment of motor coordination observed in rotarod assay	Individual compounds were not isolated from active fractions; mechanisms inferred from pharmacological models and literature correlations	Shan et al. (2016)

Table 3 continued

Part used	Preparation/Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Roots	Methanolic extraction followed by liquid–liquid partitioning and sequential chromatographic isolation	Cordoin, isocordoin, lupeol, lupenone, β -sitosterol, stigmasterol, sitosterone and very long-chain free fatty acids (C16–C42)	IR, 1D/2D NMR, ESIMS, GC–MS, TLC and column chromatography	Moderate antioxidant activity and cytotoxic activity in <i>Artemia salina</i> assay	Antioxidant activity associated with chalcones and free radical scavenging; cytotoxicity possibly related to cordoin	Methanol-soluble fraction showed significant toxicity in brine shrimp lethality assay	Biological assays restricted to in vitro antioxidant and brine shrimp models; no mammalian cytotoxicity assays or in vivo pharmacological evaluation	Cardoso et al. (2024)

distinction is relevant because extraction conditions strongly influence metabolite composition, chemical stability, bioaccessibility, and biological activity.

H. speciosa has emerged as a promising source of bioactive compounds with a broad pharmacological spectrum. An integrated analysis of the available studies highlights not only the phytochemical diversity found in different parts of the plant but also the biological relevance of the identified metabolites, many of which belong to the classes of phenolic acids, flavonoids, and triterpenes.

Among the most frequently identified compounds are chlorogenic acid and rutin, found in various extracts from the leaves, fruits, and latex of the plant (Neves et al. 2016; Torres-Rêgo et al. 2016; Bastos et al. 2017; Dos Santos et al. 2018; Bitencourt et al. 2019; Pereira et al. 2022; Martins et al. 2023; Castro et al. 2024). Chlorogenic acid has been associated with anti-inflammatory and antioxidant effects through NF- κ B pathway inhibition, cytokine modulation, and downregulation of COX-2 expression (Torres-Rêgo et al. 2016; Bitencourt et al. 2019). Rutin, in turn, stands out as a potent vasodilator and antioxidant agent, with evidence of synergistic activity with other flavonoids such as quercetin and catechin (Bastos et al. 2017; dos Santos et al. 2018; Pereira et al. 2022; Martins et al. 2023).

Leaf-derived extracts and in vitro cell suspension cultures of *H. speciosa* exhibited highly diverse phytochemical profiles, including flavonoids, phenolic acids, chalcones, procyanidins, carotenoids, and cyclitols identified by UHPLC-HRMS/MS, HPLC-DAD-MS/MS, UPLC-DAD-ESI-MS/MS, and NMR-based approaches (Bastos et al. 2017; Santos et al. 2018; Dantas et al. 2021; Pereira et al. 2022; Junior et al. 2024). These compounds have been associated with multiple pharmacological activities, including antidiabetic, antioxidant, anti-inflammatory, and wound-healing effects. Notably, studies have highlighted the potential of SGLT1/2 inhibitors (such as phloretin and phloridzin) in glycemic modulation, and vasodilatory flavonoids (quercetin, kaempferol, rutin) in the control of hypertension (Bastos et al. 2017; Pereira et al. 2022).

Aqueous decoctions and partially fractionated fruit preparations demonstrated significant anti-inflammatory efficacy in experimental models, reducing inflammatory mediators, leukocyte migration, nitric oxide production, and cytokine release, including TNF- α ,

Table 4 Comparison of phytochemical and pharmacological studies involving *Eugenia dysenterica* DC. and its different preparation/extraction systems

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Leaves	Sequential hexane, ethanolic and aqueous extraction; infusion preparation	No direct phytochemical characterization performed in this study	Gastrointestinal motility assay, serum biochemical analyses and histopathological evaluation	Antidiarrheal activity; ethanolic extract reduced intestinal motility in castor oil-induced diarrhea model	Antimotility effect; antisecretory mechanism was not supported by electrolyte data	Infusion, ethanolic and aqueous extracts caused intestinal and hepatic histopathological alterations; ALT increased but remained within reference values	Active compounds were not identified; mechanisms inferred from pharmacological responses; toxicity observed after repeated administration; no clinical validation	Lima et al. (2011)
Stem bark and leaves	Methanolic extraction followed by chromatographic isolation	3-acetyl-urs-12-en-28-oic acid, 3-acetyl-olean-12-en-28-oic acid, isoquercetin, 3-O- β -glucopyranosyl- β -sitosterol, methyl 3-hydroxy-4-methoxybenzoate, methyl 4-hydroxyphenyl propionate, E-methyl-4-hydroxycinnamate, quercetin-3-O-(6"-O-galloyl)- β -D-glucopyranoside and quercetin-3-O- β -D-galactopyranoside	ID and 2D NMR, chromatographic isolation and comparison with literature data	Antileukemic activity against CCRF-CEM and Kasumi-1 leukemia cell lines	Compound quercetin-3-O-(6"-O-galloyl)- β -D-glucopyranoside reduced cell viability, induced apoptosis/late mitochondrial depolarization, cell-cycle arrest and myeloid differentiation	No in vivo toxicological evaluation; cytotoxicity evaluated only in leukemic cell lines	Restricted to in vitro leukemia models; no selectivity assay with non-cancer cells; no in vivo validation	Vitek et al. (2017)
Leaves	Aqueous infusion followed by Sephadex LH-20 chromatographic isolation	Quercetin and catechin	HPLC-DAD, TLC, UV, IR, $^1\text{H}/^{13}\text{C}$ NMR and comparison with authentic standards	Moderate acetylcholinesterase inhibitory activity and cytotoxicity against SH-SY5Y neuroblastoma cells	ACHE inhibition observed for the aqueous extract, quercetin and catechin; neuroprotective relevance remains inferential	Aqueous extract reduced SH-SY5Y viability at concentrations above 7.8 $\mu\text{g}/\text{mL}$ after 24 h	In vitro enzyme and neuroblastoma assays only; no in vivo neuroprotective validation; mechanisms not directly tested beyond AChE inhibition and cytotoxicity	Gasca et al. (2017)

Table 4 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Leaves	Aqueous extract followed by acetone fractionation	Catechin and epicatechin previously reported as markers; tannins, flavonoids, terpenes and saponins reported for leaves	DPPH assay, MTT assay, wound-healing assay, nitric oxide assay and RT-qPCR; no direct structural characterization of the tested fraction	Antioxidant and cytoprotective effects in human gingival fibroblasts; no confirmed anti-inflammatory activity	Cytoprotection associated with antioxidant activity; minor NRF2 and SOD1 expression changes were observed without statistical significance	AFED showed low cytotoxicity to human gingival fibroblasts and reduced chlorhexidine-associated cytotoxicity	No direct structural characterization of the tested fraction; anti-inflammatory activity not confirmed; restricted to in vitro oral cell models	Costa et al. (2019)
Leaves	Aqueous extract incorporated into chitosan microparticles and dermatological emulsion	Catechin and epicatechin	TLC, HPLC-DAD/UV and comparison with authentic standards	Antimicrobial activity against <i>Staphylococcus aureus</i> ; enhanced catechin skin penetration and angiogenic activity	Activity associated with catechin-containing aqueous extract; chitosan microparticles improved catechin stability, sustained release and topical delivery	No significant cytotoxicity against HaCaT keratinocytes and L-929 fibroblasts at antimicrobial concentrations	Mainly in vitro and formulation-based study; no in vivo skin infection model; long-term dermatological safety not evaluated	Mazuti da Silva et al. (2020)
Fruits, pulp, seeds and leaves	Literature-based review of nutritional, phytochemical and pharmacological studies	Quercetin derivatives, kaempferol derivatives, ellagic acid, ellagitannins, proanthocyanidins, catechin, carotenoids, tocopherols, vitamin C, tannins, β -caryophyllene, α -humulene, γ -cadinene and organic acids	Review of previous studies using HPLC, TLC, spectrophotometry, mass spectrometry and phytochemical screening	Antioxidant, anti-inflammatory, antihyperglycemic, hypolipidemic, anti-obesity, gastroprotective, antidiarrheal, laxative and antimicrobial potential	Mechanisms discussed from literature include antioxidant effects, enzyme inhibition, NF- κ B/APK/PPAR-related pathways and microbiota modulation	Review notes intestinal and hepatic alterations after high-dose leaf preparations; fruit pulp and isolated peptide showed no relevant intestinal histopathological damage in cited studies	Narrative review based on heterogeneous studies; many mechanisms remain literature-based; limited clinical validation	Santana et al. (2022)
Leaves, fruit pulp, peel and seeds	Ethanollic extraction followed by liquid-liquid fractionation	Gallated B-type proanthocyanidins, gallic acid, quercetin, quercetin glycosides, myricetin and flavonoid derivatives	LC-ESI-MS/MS, total phenolic, flavonoid and proanthocyanidin assays; DPPH, FRAP and ORAC assays	Antioxidant, antiglycation, α -amylase inhibitory and α -glucosidase inhibitory activities	Effects associated with gallated proanthocyanidins and flavonoids; radical scavenging and possible interaction with glycoside hydrolases	Polar fractions from leaves and seeds showed low cytotoxicity at tested concentrations	Mainly in vitro biochemical assays; no in vivo diabetic validation of isolated fractions; mechanisms inferred from biochemical and LC-MS/MS evidence	Justino et al. (2022)

Table 4 continued

Part used	Preparation/ Extraction type	Identified bioactive compounds	Identification method	Pharmacological activity	Proposed mechanism of action	Toxicity and safety	Study limitations	References
Fruit by-products: peels and seeds	Ultrasound-assisted hydroethanolic extraction optimized by Box-Behnken design and response surface methodology; liquid and lyophilized bioinputs	Gallie acid, ellagic acid, tannins, anthraquinone heterosides and phenolic compounds	HPLC–DAD, phytochemical screening, total phenolic quantification, ABTS, FRAP and DPPH assays	Antioxidant, antimicrobial and antibiofilm activities against microorganisms associated with bovine mastitis and poultry contamination	Activities associated with phenolic-rich composition; specific molecular antimicrobial mechanisms were not investigated	No in vivo toxicological validation; authors recommend further safety and clinical studies	In vitro antimicrobial and antibiofilm assays only; no in vivo antimicrobial validation; phytochemical characterization restricted to selected markers	Barbosa et al. (2025)

IL-1 β , and IL-6 (Torres-Rêgo et al. 2016; Bitencourt et al. 2019). These preparations also showed protective effects against inflammatory lung injury induced by *Tityus serrulatus* scorpion venom, an effect associated with modulation of NF- κ B signaling pathways and polarization of macrophages toward the anti-inflammatory M2 phenotype (Bitencourt et al. 2019).

Studies involving the latex of *H. speciosa* have also revealed remarkable pharmacological properties. The work by Almeida et al. (2014) demonstrated the angiogenic potential of water-eluted latex, with no observed cytotoxicity, while Neves et al. (2016) reported its osteogenic activity, promoting periosteal cell proliferation and bone regeneration in an in vivo model. Although cis-1,4-polyisoprene was identified as the major constituent in the physicochemical analysis (Almeida et al. 2014), phenolic compounds such as chlorogenic acid and naringenin-7-O-glucoside were also detected in other fractions and are likely involved in the regenerative activities (Neves et al. 2016).

Notably, the latex also exhibited leishmanicidal activity, particularly the < 10 kDa fraction, which significantly reduced promastigote and amastigote forms of *Leishmania amazonensis*, with no toxic effects observed in macrophages (Castro et al. 2024). This action was attributed to the combination of carbohydrates such as galactose, which may stimulate pro-inflammatory cytokine production, and phenolic compounds with direct activity on parasite enzymes, such as arginase (Castro et al. 2024).

An innovative study using suspended cells derived from in vitro cultured leaves revealed that carbon sources such as sucrose and glucose can modulate the production of secondary metabolites through controlled osmotic stress (Dantas et al. 2021). Significant production of compounds such as rosmarinic acid, epicatechin, rutin, and quercetin highlights the potential of plant cell culture as a sustainable platform for the production of bioactives with cosmetic and pharmaceutical applications (Dantas et al. 2021).

Phenolic-rich leaf extracts obtained by sequential pressurized liquid extraction exhibited antioxidant and antibacterial activity, likely associated with free radical scavenging and disruption of bacterial membrane integrity (Barbosa et al. 2019). Complementarily, extracts from the stem bark showed no intrinsic antibacterial activity but were able to potentiate the efficacy of antibiotics such as gentamicin and

Table 5 Comparison between the four Cerrado species selected regarding representative bioactive compounds, analytical techniques used, pharmacological activities, mechanisms of action and reported toxicity

Species	Representative bioactive compounds	Identification techniques	Main pharmacological activities	Proposed mechanisms of action/ Molecular targets	Toxicity and safety
<i>Dipteryx alata</i> Vogel	Quercetin, rutin, gallic acid, procatechuic acid, luteolin, 7,8,3'-trihydroxy-4'-methoxyisoflavone, lupeol, catechin, quercetin glycosides, flavonoids, tannins and phenolic acids	TLC, HPLC–DAD, LC–DAD–MS/MS, UHPLC–MS/MS, GC–MS, PS–MS, 1H/13C NMR, HMBC, HSQC, HR–ESI–MS	Antioxidant, anti-inflammatory, antiphidic, antibacterial, cytoprotective, wound-healing, antinociceptive and selective in vitro cytotoxic activities	Inhibition of phospholipases and venom enzymes, ROS scavenging, modulation of oxidative stress, membrane stabilization, mitochondrial protection, inhibition of bacterial adhesion and biofilm formation, possible induction of apoptosis in tumor cells	Generally low toxicity in cell-based and preliminary experimental models; weak cytotoxicity toward non-tumor cell lines in some studies; long-term and clinical safety data remain limited
<i>Hancornia speciosa</i> Gomes	Chlorogenic acid, rutin, catechin, epicatechin, bornesitol, quercetin derivatives, kaempferol, procyanidins, rosmarinic acid, phlorizin, lupeol ester derivatives	HPLC–DAD, HPLC–DAD–MS/MS, UHPLC Orbitrap–HRMS/MS, UPLC–DAD–ESI–MS/MS, GC–FTD, ESI–MS/MS, NMR	Antioxidant, anti-inflammatory, antihypertensive, antidiabetic, antibacterial, osteogenic, leishmanicidal, antioesity and wound-healing potential	NF- κ B modulation, ACE inhibition, α -glucosidase inhibition, vasorelaxation, oxidative stress reduction, cytokine modulation, macrophage M2 polarization, bacterial membrane disruption	Generally low cytotoxicity in specific experimental models; low genotoxicity/mutagenicity reported in some assays; safety evidence remains preparation-dependent and long-term toxicity data are limited
<i>Bowdichia virgilioides</i> Kunth	Flavonoids, tannins, triterpenes, saponins, mackianin, medicarpin, cordoin, isocordoin, lupeol, lupenone, β -sitosterol, stigmasterol, sitostenone and VLCFAs	HPLC–DAD, GC–MS, IR, 1D/2D NMR, ESIMS, TLC, HSQC, column chromatography	Antioxidant, antinociceptive, anti-inflammatory, anxiolytic, antihyperglycemic, larvicidal and cytotoxicity in <i>Artemia salina</i> assay	COX/iNOS-related pathways, ROS scavenging, opioid/TRPV1/ glutamatergic modulation, reduction of lipid peroxidation, possible GLUT2-related modulation, larvicidal activity associated with mackianin; CDC25B inhibition remains hypothetical for prenylated chalcones	Generally low acute toxicity in specific in vivo models; no motor impairment in behavioral assays; cytotoxicity observed in <i>Artemia salina</i> assay; no long-term or clinical safety evaluation available
<i>Eugenia dysenterica</i> DC	Quercetin-3-O-(6''-O-galloyl)- β -D-glucopyranoside, quercetin, catechin, epicatechin, gallic acid, ellagic acid, proanthocyanidins, kaempferol derivatives, gallated B-type proanthocyanidins	HPLC–DAD, LC–MS/MS, LC–ESI–MS/MS, TLC, UV/Vis, 1D/2D NMR, chromatographic isolation	Antioxidant, antileukemic, antimicrobial, antglycation, α -amylase/ α -glucosidase inhibitory, antiarthral, antioesity, gastroprotective, anti-biofilm and neuropharmacological potential	Apoptosis induction, mitochondrial depolarization, radical scavenging, inhibition of AGE formation, α -amylase/ α -glucosidase inhibition, acetylcholinesterase inhibition, proposed modulation of NF- κ B-, AMPK- and PPAR-related pathways	Safety evidence is preparation- and plant-part-dependent; some fruit-derived fractions showed low cytotoxicity, whereas prolonged use of leaf preparations induced intestinal and hepatic alterations in experimental models; more long-term toxicological studies are required

norfloxacin, characterizing them as bacterial resistance modulators (da Silva et al. 2024).

The SAR analysis of the major compounds from *H. speciosa* allows elucidation of the molecular mechanisms underlying their therapeutic activities. Chlorogenic acid, one of the most recurrent metabolites in leaf, fruit, and latex extracts, consists of an ester formed between caffeic acid and quinic acid, conferring well-documented antioxidant and anti-inflammatory properties. The conjugated phenolic system of caffeic acid facilitates the scavenging of reactive oxygen species (ROS), while the quinic acid moiety enhances aqueous solubility and chemical stability, promoting gastrointestinal absorption and interaction with enzymes such as COX-2 and arginase (Wang et al. 2022a, b; Domínguez-Avila et al. 2017; Clifford et al. 2020). The conjugation of these moieties also facilitates modulation of the NF- κ B inflammatory pathway, as observed in studies with fruit extracts (Bitencourt et al. 2019; Huang et al. 2023).

Among the predominant flavonoids, rutin stands out due to its glycosylated flavonol skeleton (quercetin-3-O-rutinoside), which incorporates sugars such as rhamnose and glucose (Pannu et al. 2021; Khan et al. 2024). This glycosylation enhances the compound's stability in aqueous preparations (such as infusions), improves intestinal bioavailability, and reduces cellular toxicity while maintaining its antioxidant capacity, attributed to the presence of hydroxyl groups at the C-3' and C-4' positions of the B-ring (Alizadeh and Ebrahimzadeh 2022; Yang et al. 2023). Studies have shown that this structural configuration promotes nitric oxide-dependent endothelial vasodilation, and its combined action with quercetin, catechin, and epicatechin potentiates protective effects on the cardiovascular system and oxidative stress control (Dal and Sigrist 2016; Donadio et al. 2021).

Glycosylated chalcones, such as phloridzin—identified in leaf extracts—exhibit strong antidiabetic potential by acting as competitive inhibitors of glucose cotransporters SGLT1 and SGLT2. Their open-chain structure (distinct from classical flavonoids with a closed C-ring) confers greater conformational flexibility, while the glucose moiety linked via an O-glycosidic bond increases selectivity for intestinal and renal membrane transporters. Its aglycone, phloretin, displays greater lipophilicity and membrane penetration, and is also effective in modulating inflammatory pathways and glycemic metabolism (Donadio et al.

2021; Abouelenein et al. 2023; Marulkar and Bhatia 2024).

Finally, pentacyclic triterpenes, especially lupeol ester derivatives and related triterpenoids identified mainly in leaf and stem bark fractions, exhibit relevant anti-inflammatory and wound-healing potential (Somensi et al. 2022; Sen et al. 2024). The hydroxyl group at the C-3 position of lupeol favors interaction with nuclear receptors such as PPAR γ and with cellular membranes, thereby modulating the expression of genes associated with inflammation and tissue repair (Sharma et al. 2021).

Despite the significant advances achieved in recent decades, research on *H. speciosa* still presents relevant gaps that limit a full understanding and application of its therapeutic potential. One of the main limitations is the lack of studies that systematically correlate isolated compounds with specific biological effects in *in vivo* models, hindering the identification of reliable chemical markers and a clearer understanding of both individual and synergistic contributions of the metabolites present in crude extracts.

Furthermore, few studies employ integrative approaches based on omics techniques—such as metabolomics, proteomics, and transcriptomics—that could reveal molecular targets and metabolic pathways modulated by these compounds under complex physiological conditions.

Another critical issue is the absence of consistent data on the pharmacokinetics, metabolic stability, and oral bioavailability of the major bioactive constituents, especially in phytotherapeutic or nutraceutical formulations. Such data are crucial to enable the transition from traditional use to evidence-based applications, including the development of standardized and technologically viable products. Although several studies reported low cytotoxicity or absence of acute toxic effects in specific experimental models, the safety evidence remains fragmented and preparation-dependent, with limited information on chronic toxicity, pharmacokinetics, reproductive toxicity, hepatotoxicity, and clinical safety.

In this context, the execution of rigorous clinical trials becomes essential to validate experimentally observed effects and enable safe and effective clinical applications. There is an urgent need for controlled clinical trials that confirm the therapeutic effects in humans, taking into account individual variability, routes of administration, and potential drug

interactions. Overcoming these gaps requires a coordinated translational research agenda that integrates phytochemical, pharmacological, and clinical advances, thereby consolidating *H. speciosa* as a scientifically and therapeutically relevant bioactive source among the medicinal plants of the Cerrado.

Bowdichia virgilioides

Bowdichia virgilioides, commonly known as “sucupira-preta”, is a large tree legume widely distributed throughout the Brazilian Cerrado. Its presence has been recorded in approximately 76% of the savanna areas analyzed, with a geographic range extending from the state of Pará to São Paulo (Ratter et al. 2003; Machado et al. 2018).

In addition to its ecological relevance, the species is valued in landscaping and widely used in the production of high-quality timber. In traditional medicine, various parts of the plant—such as seeds, bark, and roots—are commonly employed for the treatment of inflammatory and infectious conditions, including rheumatism, arthritis, wounds, skin disorders, pharyngitis, and bronchitis (Machado et al. 2018).

The phytochemical diversity of *B. virgilioides* is illustrated in Fig. 3, which displays the plant image alongside the chemical structures of the representative structurally characterized compounds in the literature. Additionally, Table 3 summarizes the main pharmacological evidence associated with different plant parts, highlighting the identified bioactive compounds, analytical methods used, observed biological activities, and the limitations of the reviewed studies.

Importantly, the studies summarized in Table 3 include both traditional aqueous preparations and non-aqueous extraction systems. While some investigations used aqueous infusions followed by lyophilization, others employed hydroethanolic, methanolic, ethanolic, hexane, partitioned, or chromatographically fractionated extracts. Therefore, as in the other species reviewed, these studies should be interpreted as complementary phytochemical and pharmacological evidence rather than uniform validation of traditional medicinal infusions. This distinction is particularly relevant because extraction solvent, polarity, fractionation, and purification procedures strongly influence metabolite recovery, structural identification, and biological activity.

Available studies on *B. virgilioides* highlight a chemically heterogeneous profile, with bioactive constituents distributed across stem bark, stem inner bark, leaves, root bark, roots, and heartwood. However, the level of phytochemical resolution varies substantially among studies, ranging from preliminary phytochemical screening of aqueous infusions to NMR-, GC-MS-, and ESIMS-based structural elucidation of isolated compounds from non-aqueous fractions. This diversity reflects the species' phytochemical plasticity, with significant variations in compound distribution depending on the plant part analyzed, extraction method, and biological model employed—supporting its potential as a multitarget source of bioactive molecules.

Among the most frequently reported classes, flavonoids, tannins, triterpenes, saponins, alkaloids, and phenolic constituents are recurrently detected in stem bark, stem inner bark, leaves, and root bark preparations. Aqueous infusions of stem inner bark and leaves showed antinociceptive, anti-inflammatory, and antioxidant activities, which were associated with inhibition of inflammatory mediators, cyclooxygenase/inducible nitric oxide synthase (COX/iNOS)-related pathways, and free radical scavenging (Thomazzi et al. 2010). Hydroethanolic stem inner bark extracts also reduced lipid peroxidation and oxidative stress in resistance-trained rats, although individual compounds were not structurally identified (dos Santos et al. 2014).

Aqueous stem bark infusions also demonstrated anxiolytic-like activity after acute and sub-chronic oral treatment, without evident locomotor impairment or myorelaxant effects (Vieira et al. 2013). However, because no direct phytochemical characterization, receptor-binding assays, or neurochemical analyses were performed, the proposed involvement of alkaloids, flavonoids, triterpenoids, or resinous constituents remains speculative. Sequential hexane and methanolic extracts from root bark showed acute antihyperglycemic activity and improved oral glucose tolerance in diabetic rats, possibly through modulation of intestinal glucose absorption and GLUT2-related pathways (Silva et al. 2015). Nevertheless, the active constituents were not isolated, and the proposed mechanism remains preliminary.

In contrast to studies based mainly on crude extracts or phytochemical screening, the investigation by Bezerra-Silva et al. (2015) provided stronger

structural evidence by isolating and characterizing the isoflavonoids maackiain and medicarpin from ethanolic heartwood extracts after cyclohexane partitioning and chromatographic fractionation. These compounds were associated with larvicidal activity against *Aedes aegypti* larvae, although the precise mechanism of larvicidal action and toxicity toward non-target organisms remain unresolved.

Hydroethanolic stem bark extracts and their solvent-partitioned fractions also showed antioxidant and antinociceptive effects in formalin-, glutamate-, and capsaicin-induced orofacial pain models (Shan et al. 2016). These effects were attributed to reactive oxygen species (ROS) modulation and possible involvement of opioid, glutamatergic, and TRPV1-related pathways, but the absence of isolated active compounds limits definitive structure–activity conclusions.

The pentacyclic triterpenes lupeol and lupenone, identified in chromatographically isolated root fractions, represent structurally relevant metabolites of *B. virgilioides*. In the broader literature, these compounds have been associated with anti-inflammatory effects, including modulation of pro-inflammatory cytokines such as TNF- α and IL-1 β . However, their specific pharmacological contribution in *B. virgilioides* extracts still requires direct experimental validation (Vieira et al. 2013; Agra et al. 2013).

Additionally, phytosterols such as β -sitosterol, stigmasterol, and sitostenone were identified mainly in methanolic root extracts subjected to chromatographic isolation procedures (Cardoso et al. 2024). The C-3 ketone group in sitostenone may influence interactions with lipid- and metabolism-related nuclear targets such as LXRs and PPARs, as suggested by broader phytosterol literature (Liu et al. 2022; Brañes et al. 2024; Choe et al. 2024; Sen et al. 2024; Das et al. 2025). Although these activities are well documented in the broader literature for phytosterols and pentacyclic triterpenes, their specific pharmacological contribution in *B. virgilioides* remains insufficiently elucidated.

One of the most relevant findings was the identification of prenylated chalcones, such as cordoin and isocordoin, isolated from the roots (Cardoso et al. 2024). These molecules are characterized by an α,β -unsaturated carbonyl system and prenyl substituents on the aromatic rings, structural features that may increase lipophilicity, membrane permeability, and interaction with hydrophobic biological targets. However, in *B. virgilioides*, their biological evaluation was

restricted to moderate antioxidant activity and cytotoxicity in the *Artemia salina* assay; therefore, antitumor mechanisms such as CDC25B inhibition should be discussed only as literature-based hypotheses rather than experimentally demonstrated effects for this species.

Other notable constituents include long- and very-long-chain free fatty acids (C16–C42), identified in root extracts by Cardoso et al. (2024). Although these compounds may contribute to membrane structure and stress adaptation in plants, their pharmacological role in *B. virgilioides* remains unexplored. Particularly those with chains above C22, these molecules may play structural roles in plant membranes, contributing to resistance against water and heat stress (de Carvalho and Caramujo 2018; Batsale et al. 2021; Sharma et al. 2023). Recent studies suggest that certain fatty acids and lipid-derived metabolites may act as cellular signaling molecules by activating G protein-coupled receptors and modulating inflammatory and metabolic pathways; however, the specific biological relevance of very-long-chain fatty acids in *B. virgilioides* remains to be demonstrated (Panov et al. 2024).

From a methodological standpoint, the reviewed studies exhibit considerable heterogeneity in both extraction systems and analytical depth. Some studies directly investigated aqueous infusions followed by lyophilization, which are closer to traditional preparations, but relied mainly on phytochemical screening and pharmacological assays without structural elucidation. In contrast, studies using hydroethanolic, methanolic, ethanolic, hexane, or chromatographically fractionated extracts provided stronger structural information, including NMR-, GC–MS-, and ESIMS-based identification, but were less representative of traditional medicinal use. This methodological divergence limits direct comparisons across studies and reinforces the need for future investigations that combine ethnobotanically realistic aqueous preparations with high-resolution metabolomics and bioassay-guided fractionation.

Regarding safety, the available evidence remains incomplete and preparation-dependent. Aqueous stem inner bark extracts showed low acute toxicity, and aqueous stem bark infusions did not impair motor coordination in behavioral assays (Thomazzi et al. 2010; Vieira et al. 2013). Hydroethanolic stem bark fractions also showed no motor impairment in the rotarod assay (Shan et al. 2016). However, the methanol-soluble root fraction showed significant

toxicity in the *Artemia salina* lethality assay, highlighting the need for more comprehensive toxicological studies, including mammalian cytotoxicity, genotoxicity, chronic toxicity, reproductive toxicity, and non-target organism assessment (Cardoso et al. 2024).

Therefore, *B. virgilioides* represents a strategic phytochemical matrix with relevant anti-inflammatory, antinociceptive, anxiolytic, antihyperglycemic, larvicidal, antioxidant, and cytotoxic potential. However, the current evidence remains fragmented across heterogeneous extraction systems and uneven levels of chemical characterization. Future studies should prioritize the integration of traditional aqueous preparations with LC–MS/MS, NMR-based metabolomics, bioassay-guided fractionation, and mechanistic pharmacology to clarify which compounds are actually present in medicinal infusions and which bioactivities can be reliably attributed to them. This approach will be essential to bridge traditional knowledge, phytochemical validation, and safe biotechnological application of *B. virgilioides* metabolites.

Eugenia dysenterica

Eugenia dysenterica, commonly known as “cagaita”, is a native and endemic fruit-bearing species of the Brazilian Cerrado biome, widely distributed in the Central-West and Southeast regions of Brazil, particularly in the states of Goiás, Minas Gerais, Mato Grosso, and Mato Grosso do Sul (Alvarenga et al. 2019). This arboreal species belongs to the Myrtaceae family and predominantly occurs in typical cerrado, cerradão, and open field formations, playing a significant role in the composition of the savanna vegetation (Zucchi et al. 2003; Barbosa et al. 2015).

In addition to its ecological value, *E. dysenterica* has long been used in traditional medicine. Its leaves are commonly used to prepare infusions with antidiarrheal properties and for the treatment of jaundice, whereas its fruits—recognized for their laxative effect—are consumed fresh or processed into juices, jams, and sweets (de Sousa et al. 2018). These traditional applications highlight the plant’s relevance both for local communities and for ethnobotanical and pharmacological studies.

Figure 4 displays the image of *E. dysenterica* and the chemical structures of five representative bioactive

compounds identified in different preparation/extraction systems: (A) quercetin, (B) catechin, (C) epicatechin, (D) gallic acid, and (E) ellagic acid. These representative compounds, mostly belonging to flavonoid and phenolic acid classes, have been associated with a variety of important pharmacological activities.

Table 4 summarizes the main phytochemical and biological data from studies involving different plant parts, including extraction and identification methods, proposed mechanisms of action, toxicity assessments, and experimental limitations, providing a comprehensive overview of the therapeutic potential of *E. dysenterica*.

Importantly, the studies summarized in Table 4 include traditional aqueous preparations, such as leaf infusions and aqueous extracts, but also methanolic, ethanolic, hydroethanolic, fractionated, chromatographically isolated, and formulation-based preparations. Therefore, these studies should not be interpreted uniformly as direct evidence of traditional medicinal infusions. Instead, they provide complementary phytochemical and pharmacological evidence that helps clarify the chemical diversity, biological potential, and safety concerns associated with *E. dysenterica*. This distinction is essential because extraction solvent, fractionation, formulation strategy, and plant part strongly influence metabolite recovery, bioaccessibility, toxicity, and biological activity.

Phytochemical studies on *E. dysenterica* have revealed a highly diverse metabolic profile, although the level of chemical characterization varies substantially among preparations. Traditional aqueous preparations, such as leaf infusions and aqueous extracts, have been evaluated mainly for gastrointestinal, neuropharmacological, cytoprotective, antimicrobial, and topical effects, whereas methanolic, ethanolic, hydroethanolic, and fractionated extracts have provided more detailed structural information on flavonoids, phenolic acids, proanthocyanidins, triterpenes, sterols, and other specialized metabolites (Lima et al. 2011; Gasca et al. 2017; Costa et al. 2019; Mazutti da Silva et al. 2020; Justino et al. 2022; Barbosa et al. 2025). Advanced characterization techniques, such as one- and two-dimensional NMR, LC–MS/MS, and HPLC–DAD, have enabled the structural identification of structurally characterized compounds with recognized biological potential.

Among the structurally characterized metabolites, quercetin-3-O-(6“-O-galloyl)- β -D-glucopyranoside was isolated from methanolic extracts of stem bark and leaves after chromatographic purification and demonstrated antileukemic activity against CCRF-CEM and Kasumi-1 leukemia cell lines (Vitek et al. 2017). This compound reduced cell viability, induced apoptosis and late apoptosis-necrosis, promoted mitochondrial depolarization, and caused cell-cycle arrest. However, because this evidence derives from isolated compounds and in vitro leukemia models, it should be interpreted as complementary mechanistic evidence rather than direct validation of traditional aqueous preparations. The antiproliferative activity of quercetin-3-O-(6“-O-galloyl)- β -D-glucopyranoside is attributed to the galloyl moiety, which increases the electronic density of the molecule and enhances interactions with intracellular proteins involved in cell cycle regulation, a mechanism also observed in galloylated compounds such as pentagalloyl glucose (Wen et al. 2023).

Ethanollic extracts followed by liquid–liquid fractionation from leaves, fruit pulp, peel, and seeds revealed gallated B-type proanthocyanidins, gallic acid, quercetin, quercetin glycosides, myricetin, and other flavonoid derivatives by LC–ESI–MS/MS (Justino et al. 2022). These polar fractions showed antioxidant, antiglycation, α -amylase inhibitory, and α -glucosidase inhibitory activities, suggesting antidiabetic potential. However, these findings were restricted to in vitro biochemical assays, and no in vivo diabetic validation of isolated fractions was performed.

Aqueous leaf extracts followed by acetone fractionation also showed antioxidant and cytoprotective effects in human gingival fibroblasts, reducing chlorhexidine-associated cytotoxicity (Costa et al. 2019). However, the tested fraction was not directly structurally characterized, and anti-inflammatory activity was not confirmed, limiting mechanistic conclusions.

Formulation-based studies further demonstrated the technological relevance of aqueous leaf extracts. Chitosan microparticles and dermatological emulsions containing catechin- and epicatechin-rich aqueous extracts improved catechin stability, sustained release, skin penetration, antimicrobial activity against *Staphylococcus aureus*, angiogenic activity, and topical delivery, with low cytotoxicity toward HaCaT

keratinocytes and L-929 fibroblasts at antimicrobial concentrations (Mazutti da Silva et al. 2020). Nevertheless, these findings remain mainly in vitro and formulation-based, with no validation in in vivo skin infection models.

Ultrasound-assisted hydroethanolic extracts from fruit by-products, particularly peels and seeds, were rich in gallic acid, ellagic acid, tannins, anthraquinone heterosides, and phenolic compounds (Barbosa et al. 2025). These liquid and lyophilized bioinputs showed antioxidant, antimicrobial, and antibiofilm activities against microorganisms associated with bovine mastitis and poultry contamination. However, the antimicrobial mechanisms were not directly investigated, and in vivo toxicological and antimicrobial validation remains necessary.

A broader literature-based synthesis by Santana et al. (2022) integrated evidence from nutritional, phytochemical, and pharmacological studies involving fruits, pulp, seeds, and leaves. This review highlighted antioxidant, anti-inflammatory, antihyperglycemic, hypolipidemic, anti-obesity, gastroprotective, antidiarrheal, laxative, and antimicrobial potential, with mechanisms discussed from the literature involving enzyme inhibition, NF- κ B/AMPK/PPAR-related pathways, and microbiota modulation. However, because many of these mechanisms derive from heterogeneous studies, they should be interpreted as integrative hypotheses requiring direct validation in standardized preparations.

Toxicological evidence for *E. dysenterica* is preparation- and plant-part-dependent. Lima et al. (2011) reported that repeated administration of leaf infusion, aqueous extract, and ethanolic extract caused intestinal and hepatic histopathological alterations, although ALT levels remained within reference values. In contrast, some fruit-derived preparations and polar fractions showed low cytotoxicity in specific in vitro models, as summarized by Santana et al. (2022) and Justino et al. (2022). These contrasting findings reinforce the need to distinguish between leaves, fruits, seeds, peels, aqueous infusions, ethanolic fractions, and formulation-based preparations when discussing safety.

Aqueous leaf infusions followed by chromatographic isolation yielded quercetin and catechin, which showed moderate acetylcholinesterase inhibitory activity and cytotoxicity against SH-SY5Y neuroblastoma cells (Gasca et al. 2017). Although these

findings suggest possible neuropharmacological relevance, the aqueous extract reduced cell viability at higher concentrations, and no in vivo neuroprotective validation was performed. Despite promising preliminary evidence, the neuropharmacological potential of this species remains underexplored and demands further investigation using other cell lines and in vivo models.

In summary, *E. dysenterica* presents a complex and preparation-dependent phytochemical profile, with aqueous leaf preparations, methanolic isolates, ethanolic fractions, topical formulations, and hydroethanolic fruit by-product extracts providing heterogeneous levels of chemical and pharmacological evidence. Phenolic compounds, flavonoids, proanthocyanidins, galloylated derivatives, and phenolic acids appear to contribute to antioxidant, antimicrobial, antitrypsin, cytoprotective, antidiarrheal, antileukemic, and topical wound-related activities. Nevertheless, the current evidence remains fragmented across heterogeneous extraction systems, and future studies should prioritize standardized aqueous infusions and decoctions combined with LC–MS/MS, NMR-based metabolomics, bioassay-guided fractionation, toxicological profiling, and in vivo validation.

Comparative phytochemical profiles and bioactivities

The integrated analysis of the four native Cerrado—*D. alata*, *H. speciosa*, *B. virgilioides*, and *E. dysenterica*—reveals a highly heterogeneous yet interconnected phytochemical and pharmacological landscape shaped by differences in plant parts, extraction systems, analytical approaches, and experimental validation levels.

To synthesize this information comparatively, Table 5 provides a consolidated overview of the main identified compounds, analytical techniques employed, predominant pharmacological activities, proposed molecular mechanisms, and available data on toxicity and safety. This integrated assessment provides the foundation for a critical evaluation of the therapeutic and biotechnological opportunities associated with each species.

The comparative analysis of *D. alata*, *H. speciosa*, *B. virgilioides*, and *E. dysenterica* reveals a highly heterogeneous yet interconnected phytochemical and

pharmacological landscape shaped by distinct preparation systems, extraction solvents, analytical approaches, and experimental models. Importantly, the available evidence derives from traditional aqueous infusions and decoctions as well as hydroethanolic, methanolic, chromatographically fractionated, formulation-based, and metabolomics-oriented extraction systems. Therefore, the pharmacological activities discussed in this comparative section should be interpreted as complementary levels of phytochemical and biological evidence rather than uniform validation of traditional medicinal infusions.

All four species share a predominance of flavonoids and phenolic acids, though with structural variations and organ-specific distributions that confer distinct pharmacological profiles. In *E. dysenterica*, complex glycosylated flavonoids such as quercetin-3-O-(6“-O-galloyl)- β -D-glucopyranoside, isoquercetin, and derivatives of catechin, epicatechin, and type B proanthocyanidins are distributed across leaves, seeds, fruit pulp, peels, aqueous infusions, ethanolic fractions, and chromatographically isolated preparations (Vitek et al. 2016; Justino et al. 2022). In contrast, *H. speciosa* is characterized by a high abundance of flavonoids such as rutin, quercetin, phlorizin, and luteolin derivatives, particularly in leaves and latex, along with phenolic acids including chlorogenic and rosmarinic acids (Bastos et al. 2017; Dantas et al. 2021; Pereira et al. 2022).

D. alata exhibits a chemically diverse profile involving flavonoids, phenolic acids, methoxylated isoflavones, tannins, triterpenes, fatty acids, and lipid-associated metabolites distributed across bark, leaves, pulp, peel, almonds, seed oil, and infusion-derived preparations. However, this diversity derives from highly heterogeneous extraction systems, including hydroalcoholic bark extracts, methanol/water pulp extracts, ultrasound-assisted extraction, PS-MS metabolomic profiling, nanoemulsions, and one lyophilized leaf infusion study (Nazato et al. 2010; Puebla et al. 2010; Leite et al. 2020; Barizão et al. 2021; Nunes et al. 2024; Dos Santos et al. 2025).

With regard to the application of advanced analytical techniques, *E. dysenterica* and *D. alata* account for the largest number of compounds identified using high-resolution methods such as LC–ESI–MS/MS, UHPLC–MS/MS, HPLC–DAD, PS–MS, and one- and two-dimensional NMR spectroscopy (1H, 13C, HSQC, HMBC) (Nunes et al. 2024; Sen et al. 2024;

Vitek et al. 2016; Mazutti da Silva et al. 2020). The combination of bioactivity-guided fractionation with detailed spectral analysis has enabled not only the structural elucidation of novel compounds but also more detailed structural characterization and preliminary structure–activity interpretations, although many proposed mechanisms remain inferential and dependent on extract composition, fractionation strategy, and experimental model.

In *B. virgilioides*, although few studies have systematically employed NMR techniques, targeted investigations have identified rare compounds such as prenylated chalcones associated with moderate antioxidant activity and cytotoxicity in the *Artemia salina* assay (Bezerra-Silva et al. 2015; Cardoso et al. 2024). *H. speciosa* has made significant strides through the use of UPLC-DAD-ESI-MS/MS and studies on stress-induced metabolite production in cell suspension cultures, representing a promising and potentially sustainable approach for bioactive metabolite production (Dantas et al. 2021).

The analyzed species exhibit varying degrees of pharmacological applicability, *H. speciosa* and *E. dysenterica* show promising but still preliminary evidence for systemic applications, particularly as anti-inflammatory, hypoglycemic, and systemic antioxidant agents. These effects have been associated with proposed modulation of NF- κ B-, AMPK-, and PPAR γ -related pathways, inhibition of digestive enzymes such as α -amylase and α -glucosidase, reduction of advanced glycation end-products (AGEs), and possible regulation of gut microbiota composition (Torres-Rêgo et al. 2016; Mazutti da Silva et al. 2020; Santana et al. 2022; Justino et al. 2022).

In contrast, *D. alata* and *B. virgilioides* are notable for their antioxidant, anti-inflammatory, antio-phidic, antinociceptive, larvicidal, cytoprotective, and wound-related activities, depending on the plant part and extraction system evaluated. Experimental studies have reported epithelial regeneration, inhibition of inflammatory mediators (COX-2, TNF- α), antimicrobial activity against resistant pathogens, and larvicidal and antivenom efficacy have been reported in several studies (Thomazzi et al. 2010; Bezerra-Silva et al. 2015; Mazutti da Silva et al. 2020; da Silva et al. 2024). The use of nanotechnological formulations, such as chitosan microparticles containing *E. dysenterica* extract, has demonstrated the potential for controlled catechin release, improved skin

permeation, and angiogenic activity in formulation-based experimental systems (Mazutti da Silva et al. 2020).

The integrated analysis of these four Cerrado species also reveals a remarkable functional convergence among their identified metabolites and extract-associated compounds. Among the antioxidants, widely distributed compounds such as quercetin, rutin, gallic acid, chlorogenic acid, catechin, and epicatechin are recurrently identified among the studied species.

These metabolites may act synergistically to neutralize reactive oxygen species (ROS), protect biomolecules from lipid peroxidation and protein damage, and stabilize cellular membranes by modulating lipid fluidity and mitochondrial integrity (Stagos 2019; Gasmi et al. 2022; Yu et al. 2023; Andrés et al. 2024). The presence of multiple hydroxyl groups on aromatic rings in these flavonoids significantly contributes to their high electron-donating capacity, metal chelation ability, and inhibition of oxidative enzymes such as NADPH oxidase and xanthine oxidase (Parcheta et al. 2021; Shen et al. 2022).

Within the anti-inflammatory group, aglycone flavonoids and pentacyclic triterpenes—including flavonoids, phenolic acids, proanthocyanidins, bornesitol, and selected triterpenoids such as lupeol—stand out for their role in inhibiting the inflammatory signaling pathway mediated by NF- κ B. These compounds have been associated with reduced expression of pro-inflammatory enzymes such as COX-2 and LOX, as well as cytokines including TNF- α and IL-1 β (Zhu et al. 2017; Wu et al. 2022; Jain et al. 2022).

Mechanistically, many of these effects have been proposed to involve activation of nuclear receptors such as PPAR γ , which regulates the expression of anti-inflammatory genes and promotes macrophage polarization toward the M2 phenotype, associated with tissue repair and regeneration (Hassanshahi et al. 2022). The high biological activity of flavonoids is largely attributed to the presence of conjugated systems and phenolic hydroxyl groups in their structures, which favor specific molecular interactions, such as hydrogen bonding and hydrophobic interactions with the catalytic domains of target proteins. These interactions are essential for enzyme inhibition, receptor modulation, and the regulation of cellular signaling pathways, granting these compounds a broad spectrum of therapeutic actions (Ullah et al. 2020).

The antidiabetic effects observed in *H. speciosa* and *E. dysenterica* are predominantly attributed to flavonoids. These compounds appear to contribute significantly in the management of type 2 diabetes primarily through the inhibition of α -amylase and α -glucosidase enzymes, thereby reducing glucose absorption and postprandial glycemic peaks (Jin and He 2022; Ke et al. 2023). In addition, flavonoids may modulate signaling pathways such as IRS/PI3K/AKT and AMPK/GLUT4, potentially enhancing glucose uptake and insulin sensitivity (Ye et al. 2023; Wang et al. 2024). They also exert anti-inflammatory and antioxidant effects, protect pancreatic β -cells, and regulate gut microbiota, contributing to overall improvement of glycemic metabolism (Yang et al. 2021; Wang et al. 2022a, b; Maity et al. 2022).

Prenylated chalcones and isoflavonoids such as cordoin, isocordoin, maackiain, and medicarpin represent chemically distinctive metabolites in *B. virgilioides*. In the broader literature on prenylated flavonoids, these structural classes have been associated with antiproliferative, enzyme-modulating, and apoptosis-related activities, particularly due to prenylation and methoxyl substituents that increase lipophilicity and membrane permeability (Bartmańska et al. 2018). However, for *B. virgilioides*, the currently available biological evidence remains limited mainly to larvicidal activity and cytotoxicity in the *Artemia salina* assay, and antitumor mechanisms should therefore be interpreted as literature-based hypotheses rather than experimentally demonstrated effects for this species.

Finally, although less extensively studied, neuropharmacological effects have shown promising preliminary evidence. Flavonoids such as quercetin and catechin, isolated from *E. dysenterica*, exhibited inhibitory activity against acetylcholinesterase (AChE), with IC_{50} values below 50 $\mu\text{g/mL}$, as well as antioxidant properties that mitigate neuronal oxidative stress (Gasca et al. 2017). The ability of these compounds to cross the blood–brain barrier and modulate pathways associated with neuronal survival—such as the PI3K/Akt pathway and the upregulation of brain-derived neurotrophic factor (BDNF—suggests that their neuropharmacological potential deserves further investigation in more physiologically relevant in vivo and translational models, including experimental models relevant to neurodegenerative

disorders such as Alzheimer's and Parkinson's disease (Bellavite 2023).

Collectively, these functional groupings highlight the therapeutic versatility of secondary metabolites derived from Cerrado species, whose structural diversity may enable modulation of multiple molecular targets and metabolic pathways. The wide range of biological effects—from cytoprotective antioxidant action to cytotoxic and antiproliferative potential—confers considerable pharmacological and biotechnological potential to the species analyzed, supporting their potential as natural platforms for the development of novel multifunctional therapeutic agents.

Regarding toxicological assessments, significant differences were observed among the species. *D. alata* and *H. speciosa* generally showed low toxicity in specific experimental models, with low cytotoxicity and no significant adverse effects reported in animal or cell-based models (Leite et al. 2020; Martins et al. 2023). In contrast, studies involving aqueous leaf infusions of *E. dysenterica* revealed hepatic and intestinal lesions in rodents, indicating potential risks associated with prolonged use of traditional aqueous extracts (Lima et al. 2011). In the case of *B. virgilioides*, although several studies reported acceptable tolerability within the evaluated experimental conditions, isolated compounds from the roots showed significant cytotoxicity in *Artemia salina* bioassays, underscoring the need for further genotoxicity testing and systemic safety evaluations (Cardoso et al. 2024).

Overall, the comparative analysis reinforces the central methodological limitation identified throughout this review: most phytochemical and pharmacological evidence available for Cerrado medicinal species derives from heterogeneous extraction systems rather than standardized traditional infusions or decoctions. Future investigations should therefore prioritize ethnobotanically realistic aqueous preparations integrated with LC–MS/MS and NMR-based metabolomics, bioassay-guided fractionation, chronic toxicological evaluation, and in vivo validation. Such an approach will be essential to clarify which metabolites are actually present in traditional preparations and which biological effects can be reliably associated with their traditional medicinal use.

Research gaps, methodological challenges, and biotechnological valorization of Cerrado species

Although recent advances in the phytochemical characterization of *D. alata*, *H. speciosa*, *B. virgilioides*, and *E. dysenterica* have significantly expanded our understanding of their bioactive constituents and pharmacological activities, methodological and scientific challenges still hinder the consolidation of their therapeutic and biotechnological applications. The reviewed literature indicates that most studies remain focused on descriptive analyses, relying on conventional extraction methods, isolated in vitro assays, and partial compound characterizations, without substantial progress in integrating chemistry, pharmacology, and molecular biology.

A particularly important limitation identified throughout this review concerns the underutilization of traditional ethnobotanical knowledge as a basis for therapeutic target selection and experimental design. Although the medicinal use of Cerrado species is strongly associated with aqueous infusions and decoctions prepared according to traditional practices, a substantial portion of the available phytochemical and pharmacological evidence derives from methanolic, ethanolic, hydroethanolic, fractionated, or isolated-compound approaches that do not necessarily reproduce these traditional preparation systems. According to Cordell (2014), different extraction and preparation procedures can drastically alter the metabolite profile and, consequently, the biological outcomes associated with medicinal plant preparations.

More recent studies have similarly highlighted that aqueous extracts remain comparatively underexplored despite their central importance in traditional medicine and community-based healthcare systems (Hoel et al. 2024; Albino 2025). This limitation was also evident throughout the present review, since relatively few studies investigated standardized aqueous infusions or decoctions under conditions that realistically approximate traditional preparation methods.

Consequently, several metabolites and pharmacological activities described for *Dipteryx alata* Vogel, *Hancornia speciosa* Gomes, *Bowdichia virgilioides* Kunth, and *Eugenia dysenterica* DC. may not fully represent the chemical composition or biological effects of the preparations traditionally consumed by local populations. Future studies should therefore

prioritize ethnobotanically realistic preparation protocols combined with advanced analytical techniques and bioassay-guided approaches to better establish the relationship between traditional use, phytochemical composition, and pharmacological activity.

Another important limitation is the limited number of studies adopting integrated approaches that combine phytochemical profiling, mechanistic pharmacology, toxicology, and ethnobotanically realistic preparation methods. This is reflected in the scarcity of data concerning biosynthetic pathways, metabolic stability, synergistic interactions among compounds, and detailed molecular mechanisms of action.

Although techniques such as HPLC–DAD, GC–MS, and NMR have been applied in several studies, few have explored the combined use of high-resolution metabolomics, molecular modeling, bioassay-guided fractionation, or molecular docking—strategies now considered essential for the functional validation of natural metabolites.

Furthermore, there is a noticeable lack of standardization in extraction protocols, infusion preparation, and pharmacological testing, which compromises reproducibility and hinders cross-study comparisons. In many cases, extracts are evaluated in crude form without directed fractionation or isolation of major compounds, which prevents the identification of reliable chemical markers for clinical or industrial use. Even when compounds are isolated, they are rarely followed by pharmacokinetic, long-term toxicity, or bioavailability studies, significantly limiting their translation into the development of phytotherapeutic or nutraceutical products.

In light of these challenges, a set of methodological and strategic guidelines is proposed to guide the next generation of studies on medicinal plants from the Brazilian Cerrado:

1. Integration of untargeted metabolomics with bioassay-guided fractionation, aimed at prioritizing compounds with relevant biological activity through correlation between chemical profiles and cellular responses. Tools such as LC–MS/MS combined with multivariate analysis (PCA, OPLS-DA) and validation through functional assays should be routinely incorporated.
2. Application of molecular modeling and docking techniques to predict the affinity of natural compounds for specific pharmacological targets,

including inflammatory enzymes (COX-2, LOX), nuclear receptors (PPAR γ , LXR), ion channels, and protein kinases. These approaches may guide the rational selection of fractions or structural derivatives with greater selectivity and bioactivity.

3. Functional transcriptomic and proteomic studies capable of elucidating intracellular pathways modulated by metabolites, thereby establishing connections between chemical structure and biological response at the molecular level. This will allow the validation of mechanisms suggested in in vitro models and broaden understanding of potential side effects and pleiotropic actions.
4. Implementation of standardized in vivo assays with toxicological validation in murine, zebrafish, or *Caenorhabditis elegans* models, particularly for isolated compounds of high purity (e.g., medicarpin, cordoin, and quercetin-3-O-(6“-O-galloyl)- β -D-glucopyranoside), which have shown promising activities but still lack in-depth pre-clinical evaluation.
5. Reappraisal of traditional ethnobotanical knowledge, which remains underutilized as a basis for therapeutic target selection. The popular use of herbal infusions for digestive, respiratory, and musculoskeletal conditions, for instance, could be further explored through the identification of active compounds in teas and studies on their stability, synergism, and intestinal metabolism.

In addition to methodological strategies, it is essential to consider the ecological and conservation dimensions involved in the use of native Cerrado species. Despite hosting over 12,000 vascular plant species, the Cerrado faces high rates of deforestation, habitat fragmentation, and conversion to agricultural monocultures. Several species studied here, such as *D. alata* and *B. virgilioides*, occur in regions under intense anthropogenic pressure and are experiencing accelerated loss of natural habitats (Colli et al. 2020).

Thus, the biotechnological valorization of the Cerrado must be linked to sustainable practices and the conservation of native species, promoting ethical bioprospecting, sustainable management of wild populations, and the cultivation of species in agroforestry systems or productive home gardens. Domestication and vegetative propagation projects should accompany phytochemical research, ensuring biomass replenishment and the continuous supply of high-

quality raw material for pharmaceutical and industrial purposes.

Finally, the Cerrado should be regarded not only as a reservoir of biodiversity but as a strategic phytochemical heritage, whose scientific exploration demands interdisciplinary approaches, international cooperation, and public policies that support applied science, conservation, and the sustainable use of its medicinal flora.

Conclusions

This review presented a comprehensive and critical comparative analysis of the phytochemical composition and pharmacological activities of four native Cerrado species widely used in medicinal infusions: *D. alata*, *H. speciosa*, *B. virgilioides*, and *E. dysenterica*. The collected evidence reveals that these species harbor a remarkable diversity of bioactive secondary metabolites, including glycosylated flavonoids, phenolic acids, isoflavones, triterpenes, proanthocyanidins, and prenylated chalcones, many of which have been identified and structurally characterized using high-resolution analytical techniques such as LC–MS/MS, GC–MS, and multidimensional NMR spectroscopy.

The identified compounds exhibited a broad pharmacological spectrum, including antioxidant, anti-inflammatory, hypoglycemic, cytoprotective, antimicrobial, larvicidal, and antitumor activities, mediated through relevant molecular targets such as NF- κ B, PPAR γ , COX-2, α -glucosidase, CDC25B, and AMPK. These activities are consistent with the traditional uses of these species, highlighting the potential of integrating ethnobotanical knowledge with modern phytochemical research.

However, significant challenges remain. Most studies are still limited to crude extracts and in vitro assays, with a notable scarcity of systematic in vivo experiments, lack of long-term toxicological assessments, and insufficient pharmacokinetic data. Furthermore, only a few compounds have been individually evaluated for their bioactivity and stability, limiting the establishment of robust structure–activity relationships. The standardization of extraction protocols and the application of integrated—such as untargeted metabolomics, bioassay-guided fractionation, and

molecular modeling—are critical steps to overcome these limitations.

Additionally, the biotechnological valorization of these species must be intrinsically linked to the conservation of the Cerrado, one of the most biodiverse yet critically threatened biomes in the world. The sustainable exploitation of native medicinal plants requires not only analytical and pharmacological advances but also public policies for preservation, ethical resource management, and the promotion of applied scientific research.

In this context, this work provides a solid scientific foundation for future investigations focused on the discovery of novel multifunctional phytochemicals, contributing to the rational and sustainable use of the Brazilian Cerrado's biodiversity as a strategic reservoir of high-value bioactive molecules for therapeutic applications.

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Declarations

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

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