Received: 5 March 2026 | Revised: 14 May 2026 | Accepted: 16 June 2026

DOI: 10.1111/bph.70589

THEMED ISSUE REVIEW

Translating Brazilian medicinal plants into therapeutic innovation: Preclinical evidence and lessons learned

João Vitor A. Hoepers[1,2] | Letícia C. N. Takasumi[1] | João B. Calixto[1]

[1]Centro de Inovação e Ensaios Pré-Clínicos (CIEnP), Florianópolis, Santa Catarina, Brazil

[2]Departamento de Farmacologia, Universidade Federal de Santa Catarina (UFSC), Florianópolis, Santa Catarina, Brazil

Correspondence
João B. Calixto, Centro de Inovação e Ensaios Pré-Clínicos (CIEnP), Avenida Luiz Boiteux Piazza, 1502, Cachoeira do Bom Jesus, Florianópolis, SC 88056-000, Brazil.
Email: joao.calixto@cienp.org.br

Funding information
Conselho Nacional de Desenvolvimento Científico e Tecnológico; Financiadora de Estudos e Projetos; Ministério da Saúde; Ministério da Ciência, Tecnologia e Inovação; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina

This review critically examines more than four decades of research and innovation conducted by our research group on bioactive constituents and standardized extracts from Brazilian medicinal plants. It integrates phytochemical and preclinical pharmacological evidence, limited clinical studies and translational experiences, highlighting major scientific achievements and the persistent gap between academic research and the development of innovative phytomedicines in Brazil. In parallel, we analyse the evolution of the Brazilian phytomedicine market and regulatory advances aimed at supporting the development of phytotherapeutic agents based on scientific evidence of efficacy and safety. Despite Brazil's exceptional biodiversity and the extensive experimental data generated over several decades on medicinal plants, the translation of scientific knowledge into registered and innovative phytotherapeutic agents remains limited. This review identifies major structural barriers that continue to hinder progress, including the low engagement of the national pharmaceutical industry in innovation-driven drug development, regulatory and operational challenges related to clinical trials, and the absence of sustained governmental policies to support long-term basic and translational research. Collectively, these factors restrict Brazil's capacity to develop medicines domestically and to strategically capitalize on its biological resources. By critically reflecting on lessons learned from our long-term research and innovation efforts, this article underscores the need for integrated strategies aligning scientific excellence, regulatory frameworks, industrial participation and public policies. Strengthening these connections is essential to transform Brazil's medicinal plant biodiversity into clinically validated, safe and accessible therapeutic products that benefit public health and national innovation.

KEYWORDS
drug development, innovation, medicinal plants, non-clinical and clinical trials, phytotherapeutic medicine, regulatory framework

Abbreviations: ACEs, angiotensin-converting enzymes; Anvisa, Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária); BK, bradykinin; CREB, cAMP response element-binding protein; DSS, dextran sulfate sodium; EMA, European Medicines Agency; GLP, Good Laboratory Practice; IBD, inflammatory bowel disease; MCP-1, monocyte chemoattractant protein-1; MIP-2, macrophage inflammatory protein-2; RDC, Anvisa Collegiate Board Resolution (Resolução da Diretoria Colegiada); TNBS, trinitrobenzene sulfonic acid; TPA, 12-*O*-tetradecanoylphorbol-13-acetate.

1 | INTRODUCTION

The use of medicinal plants predates written records and has played a central role in human health for millennia. Historical evidence indicates that species such as poppy (*Papaver somniferum*) and cannabis (*Cannabis sativa*) were already used for medicinal purposes more than 4000 years ago (Atanasov et al., 2015). However, scientific characterization of plant-derived compounds began only in the 19th century, after Friedrich Sertürner isolated morphine from poppy latex, marking a key milestone in pharmacology (Devereaux et al., 2018). This discovery established the basis for modern research of natural products and stimulated the identification of several bioactive molecules that remain clinically relevant, including morphine, codeine, papaverine, atropine, caffeine and digoxin (Calixto et al., 2000). Then, the isolation of salicin from *Salix alba* and the synthesis of acetylsalicylic acid (aspirin) in 1897 represented another decisive advance that consolidated the modern pharmaceutical industry (Montinari et al., 2019).

Natural products remain relevant in contemporary drug discovery and therapeutic practice. About 30% of currently approved medicines derive direct or indirectly from natural sources, a proportion that rises to nearly 60% in oncology (Newman & Cragg, 2020). Advances in analytical chemistry, molecular biology and synthetic methods have further elevated the importance of natural molecules as active substances and structural templates for the development of innovative drugs (Atanasov et al., 2021).

Within this global context, Brazil stands out for its remarkable biological diversity, comprising approximately 20% of the world's plants (REFLORA, 2026). This vast biodiversity constitutes a strategic reservoir of natural compounds with potential pharmacological relevance. Many active substances have already been isolated from Brazilian species, reflecting both the country's ecological richness and its strong cultural tradition of medicinal plant use (see Dutra et al., 2016, for review).

Over the past four decades, our research group has contributed to the systematic investigation of Brazilian medicinal plants, aiming to identify bioactive compounds of therapeutic interest. In a previous review (Dutra et al., 2016), we examined preclinical and clinical findings from Brazilian and international studies and the development of the national plant medicine market. Building on the previous analysis, this review article summarizes over four decades of experience from our research group in the study of Brazilian medicinal plants, focusing on their potential for the development of innovative therapies. In addition, this review explores the major scientific, regulatory and structural challenges that have limited the effective translation of Brazil's rich biodiversity into innovative medicines.

2 | OVERVIEW ON MEDICINAL PLANTS IN BRAZIL

2.1 | Brazilian market of plant-based medicines (phytotherapeutics)

The Brazilian phytotherapeutic market, valued at about 0.4 billion US dollars in 2024, represents about 2% of the Brazilian pharmaceutical market, valued at about 30 billion US dollars (IQVIA, 2025). Brazil's plant-derived medicine market share remains minimal despite containing around 20% of the world's plant species (REFLORA, 2026).

Table 1 summarizes the 20 best selling phytotherapeutic agents in Brazil in 2024. Only three were developed by Brazilian companies in collaboration with Brazilian researchers: Acheflan® (*Cordia verbenacea*), Sintocalmy® (*Passiflora incarnata*; an incremental innovation) and Melagrião® (*Mikania glomerata*) (Calixto, 2019). The remaining leading products are mostly imported, predominantly from Europe and Asia. Acheflan® and Sintocalmy® were approved by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária) (Anvisa) in 2004 (Aché Laboratórios Farmacêuticos S.A., 2025a) and 2007 (Aché Laboratórios Farmacêuticos S.A., 2025b), respectively, while Melagrião® was developed decades ago with subsequent validation of its preclinical safety and efficacy profile (Anvisa, 2014). Although Brazil has about 350 phytotherapeutic products registered in Anvisa (Anvisa, 2025), a gap between knowledge generation and market translation persists, reflecting broader challenges in converting research on Brazilian medicinal plants into clinical applications.

2.2 | Research on phytotherapeutic medicines derived from Brazilian biodiversity

As previously reported (Dutra et al., 2016), Brazilian research on national medicinal plants is of great interest and expanded substantially between 2015 and 2025. In this period, Brazilian scientists published over 63,000 scientific papers in indexed journals on plants, namely, medicinal plants (Figure 1). However, despite the growing body of scientific evidence, the innovation and development of marketable products remained limited. The absence of clear regulatory frameworks, insufficient financial and structural support, and lack of interest of Brazilian pharmaceutical companies represent the main constraints to innovation. This scenario will be illustrated by this review with investigations of endemic species with established pharmacological potential that did not reach the clinic.

2.3 | *Mandevilla velutina*: Historical and scientific relevance in Brazilian natural product studies

M. velutina (Apocynaceae), an endemic Brazilian plant, has been investigated since the early 1980s for its traditional use in treating envenomation from *Bothrops jararaca* bites and inflammatory conditions. This research occurred within a remarkable historical context: the discovery of **bradykinin** (BK) in 1949 by Maurício Rocha e Silva and collaborators (Rocha e Silva et al., 1949), by the action of *B. jararaca*'s venom. Professor Maurício Rocha e Silva, in collaboration with Wilson Beraldo and Gastão Rosenfeld, conducted seminal studies in which *B. jararaca* venom was administered to dogs. These experiments led to the identification of a plasma-derived factor responsible for a marked decrease in blood pressure and for strong contractions of isolated guinea pig ileum (Rocha e Silva et al., 1949). The authors demonstrated, for the first time, that the venom did not act directly, but

TABLE 1 Top 20 Brazilian phytomedicine products by sales, 2024 (millions of US dollars).

Ranking	Products	Active principle	Pharmaceutical companies	2024 (USD)
1	Tamarine	*Senna alexandrina* + *Cassia fistula*	Farmasa	24.14
2	Seakalm	*Passiflora incarnata*	Natulab	23.37
3	Kaloba	*Pelargonium sidoides*	Takeda	16.80
4	Forfig	*Silybum marianum*	Eurofarma	13.43
5	Flebon	*Pinus pinaster*	Farmoquímica	12.61
6	Eparema	*Peumus boldus* + *Frangula purshiana* + *Rheum palmatum*	Takeda	10.62
7	Abrilar	*Hedera helix*	Farmoquímica	9.20
8	Melagrião	*Mikania glomerata* + *Polygala senega* + *Cephaelis ipecacuanha*	Catarinense Pharma	9.04
9	Pasalix	*Crataegus oxyacantha* + *P. incarnata* + *Salix alba*	Marjan Farma	7.83
10	Naturetti	*S. alexandrina* + *C. fistula*	Sanofi-Aventis	7.59
11	Motore	*Curcuma longa*	Aché	7.41
12	Acheflan	*Cordia verbenacea*	Aché	7.09
13	Metamucil	*Plantago ovata*	Procter & Gamble	6.77
14	Arpadol	*Harpagophytum procumbens*	Apsen Farmacêutica	6.63
15	Sintocalmy	*P. incarnata*	Aché	6.59
16	Maracugina PI	*P. incarnata*	Hypera Pharma	5.95
17	Hepatilon	*P. boldus*	Kley Hertz Farmacêutica	5.95
18	Piascledine	*Persea americana* + *Glycine max*	Abbott	5.88
19	Calman	*C. oxyacantha* + *P. incarnata* + *S. alba*	Ativus	5.65
20	Vecasten	*Melilotus officinalis* + *Aesculus hippocastanum*	Marjan Farma	5.40

Note: Annual 2024 average: 1 USD = 5.39 BRL.
Source: IQVIA (report).

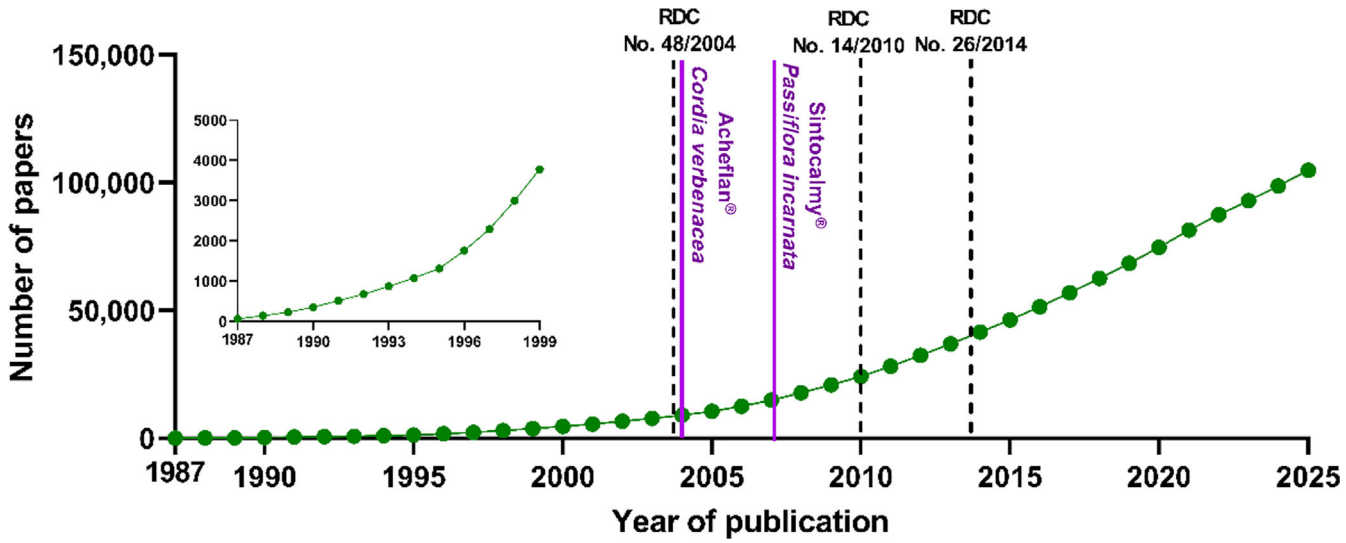


FIGURE 1 Number of papers published by Brazilian scientists on plants in the life and health sciences over the past 38 years in indexed journals. The inset indicates the number of published articles from 1987 to 1999 on an expanded scale. Black dashed lines indicate the dates of approval of Anvisa Collegiate Board Resolutions (RDCs) related to phytotherapy in Brazil. The purple lines indicate the dates of Anvisa approval of selected phytotherapeutic agents. Search strategy: TITLE-ABS-KEY (plants) AND SUBJAREA (medi OR nurs OR vete OR dent OR heal OR mult OR agri OR bioc OR immu OR neur OR phar) AND LIMIT-TO (AFFILCOUNTRY, 'Brazil'). Search performed on 8 January 2026. *Source*: Scopus.

rather triggered the formation of a vasoactive peptide in plasma through the activation of an endogenous enzymatic cascade. This peptide was later named bradykinin, and the underlying mechanism became known as the kallikrein–kinin system. This pioneering discovery opened new avenues for research into inflammatory, pain, vascular and cardiovascular mediators (Rocha e Silva et al., 1949).

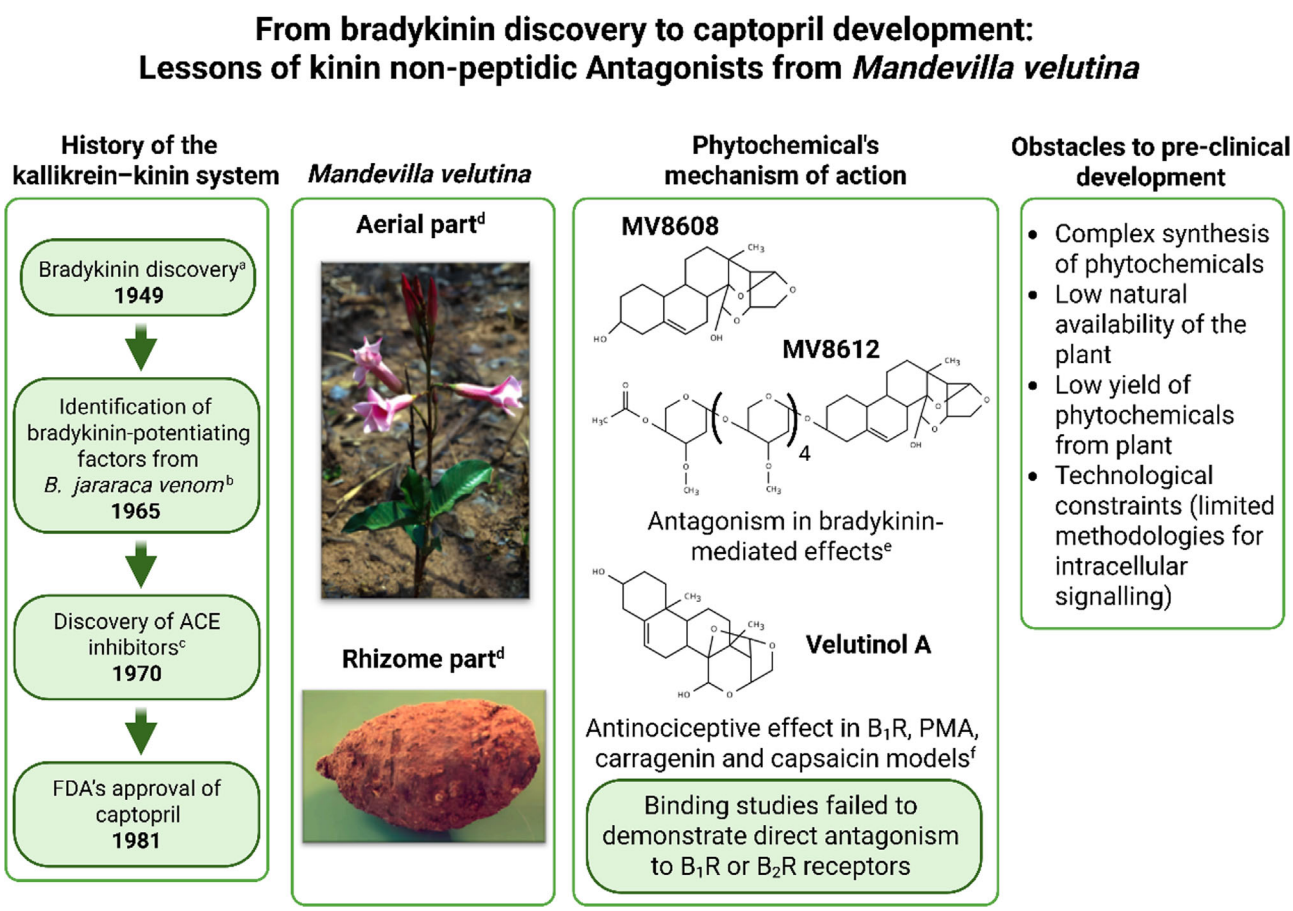


FIGURE 2 Relationship between kallikrein–kinin system discovery and *Mandevilla velutina* plant research in Brazil. [a]Rocha e Silva et al. (1949). [b]Ferreira (1965). [c]Ferreira et al. (1970). [d]Silva et al. (2025). [e]Calixto et al. (1992). [f]Mattos, Ferreira, et al. (2006).

Subsequently, in the early 1960s, Sérgio Henrique Ferreira, a PhD student under Rocha e Silva's supervision, identified peptides from *B. jararaca* venom that enhanced the hypotensive and contractile BK effects by inhibiting its degradation (Ferreira, 1965), introducing the concept of indirect modulation of endogenous mediators. Ferreira's postdoctoral work in the laboratory of Sir John Vane in London showed that these BK-potentiating peptides inhibited angiotensin-converting enzymes (**ACE**s) (Ferreira et al., 1970). This conceptual framework led to the rational design of **captopril**, the first orally active ACE inhibitor, approved for clinical use in the late 1970s (Ondetti et al., 1977). For more details on this interesting discovery that led to the development of a class of antihypertensive drugs, see the review of Calixto (2019).

Investigations of *M. velutina* directly paralleled this seminal kinin research, seeking to identify natural non-peptidic antagonists of BK-mediated responses. Plants of the genus *Mandevilla* are native to the Brazilian Cerrado and include species traditionally known as *jalapa* (see Figure 2). Their rhizomes have long been used in Brazil as an empirical remedy against snake venom, particularly bites from *B. jararaca*. *M. velutina* has been extensively investigated by our research group since the early 1980s from both chemical and preclinical pharmacological perspectives (Calixto et al., 1985, 1987; Calixto & Yunes, 1986, 1991a). This section summarizes the main experimental findings related to the BK antagonistic properties of *M. velutina*, as well as its anti-inflammatory, antinociceptive and antivenom activities (see Figure 2).

Phytochemical studies enabled the isolation and characterization of pregnane glycosides, MV8608 and MV8612, and velutinol A, from *M. velutina* rhizomes (Calixto & Yunes, 1991b; Mattos, Campos, et al., 2006). Preclinical evidence demonstrated that the hydroalcoholic extract from *M. velutina* rhizomes reduced inflammatory responses in mice arachidonic acid-induced ear oedema. MV8608 and MV8612 were also effective in inhibiting phospholipase A_2 (**PLA_2**)-dependent pro-inflammatory actions in paw oedema models induced by snake venom PLA_2 (Neves et al., 1993) and reduced the pathophysiological effects of *Crotalus durissus* and *Bothrops* venoms, validating traditional antivenom use (Biondo et al., 2003). Also, both compounds selectively inhibited BK-induced contractility in isolated guinea pig tracheal tissue without affecting responses to histamine, carbachol or prostaglandins, indicating functional selectivity for the kinin pathway (Calixto et al., 1992). These findings provide a rationale for the traditional use of *M. velutina* in snake envenomation, and inflammatory processes highlight its potential translational relevance.

In parallel, velutinol A exhibited a distinct pharmacological profile, selectively inhibiting the nociceptive response caused by the bradykinin **B_1 receptor** agonist des-Arg^9-BK, without affecting **B_2**

receptor-mediated responses or prostaglandin-mediated pain (Mattos, Campos, et al., 2006). However, binding studies failed to demonstrate direct orthosteric interaction of these compounds with kinin receptors B_1 and B_2, indicating non-classical antagonism via alternative molecular mechanisms. These mechanisms remained incompletely elucidated due to technical limitations in investigating interactions between small non-peptidic molecules and peptide-mediated intracellular signalling pathways during the period of investigation.

Despite early interest from some multinational pharmaceutical companies and initial efforts to develop these compounds as drug prototypes, translational progress was constrained by several factors. These included the structural complexity of the pregnane glycosides, limited feasibility of large-scale chemical synthesis and restricted availability of plant material. Moreover, environmental degradation of the Brazilian Cerrado for large-scale cultivation of soybeans, corn and other products further reduced access to *M. velutina*, ultimately preventing advancement to late preclinical or clinical development.

The body of work on *M. velutina* illustrates how Brazilian biodiversity, traditional knowledge and experimental pharmacology have converged to generate original insights into inflammatory and nociceptive mechanisms. The hydroalcoholic extract of its rhizomes and the isolated pregnane glycoside compounds were among the earliest evidence of the non-peptidic natural products shown to selectively modulate peptide-mediated pathways, particularly those associated with BK. Within the historical context of BK discovery in Brazil and the subsequent development of kinin pharmacology, studies on *M. velutina* contributed not only to conceptual advances but also to the training of researchers in pharmacology and natural products chemistry.

Nevertheless, the consistency, originality and conceptual relevance of the findings justify renewed translational investigation. Advances in molecular biology, receptor pharmacology and functional screening technologies now provide opportunities to revisit these compounds, clarify their molecular targets and reassess their therapeutic potential. In this context, *M. velutina* remains a compelling example of how Brazilian medicinal plants can inspire innovative pharmacological concepts with potential future clinical impact.

2.4 | *Euphorbia tirucalli*

E. tirucalli is native to Africa, particularly to the arid and semi-arid regions of the continent. The species was introduced into Brazil through early maritime routes, most likely in the late 19th century. Following its introduction, *E. tirucalli* came to be widely cultivated as a living fence and ornamental plant, as well as for property demarcation, adapting successfully to the tropical and subtropical regions of the country, especially in the North and Northeast. This plant has been used in Brazil for folk practice for the management of syphilis, asthma, rheumatism, cancer and skin tumours (Betancur-Galvis et al., 2002). The latex of *E. tirucalli* consists predominantly of water (50%–80%) and a complex mixture of bioactive constituents, including tigliane-type diterpenes (phorbol esters), ingenane derivatives (ingenol esters), and several terpenic alcohols such as euphol, β-euphorbol, taraxasterol and tirucallol (Table 2) (De Souza et al., 2019; Silva et al., 2007). Our group previously demonstrated that euphol, the major pentacyclic triterpene present in the latex of *E. tirucalli*, exerts marked anti-inflammatory and immunomodulatory effects following oral administration in rodents (Dutra et al., 2012, 2015). Euphol also prevented and ameliorated experimental colitis induced by dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS) (Dutra et al., 2011). These effects were associated with the suppression of pro-inflammatory mediators, including interleukin-1β (**IL-1β**), chemokine C–X–C motif ligand 1 (**CXCL1**)/keratinocyte-derived chemokine (KC), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-2 (MIP-2), tumour necrosis factor-α (**TNF-α**), interleukin-6 (IL-6), inducible nitric oxide synthase (**iNOS**), vascular endothelial growth factor (**VEGF**), Ki-67, adhesion molecules and nuclear factor-κB (**NF-κB**) signalling (Dutra et al., 2011).

Moreover, euphol reduced clinical and histopathological manifestations in experimental models of multiple sclerosis and inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear oedema, an effect linked to inhibition of CXCL1/MIP-2, extracellular signal-regulated kinase (**ERK**), cyclooxygenase 2 (**COX-2**) and protein kinase C (**PKC**) pathways (Dutra et al., 2012; Passos et al., 2013) (see Table 2). Collectively, these findings identify euphol as a pharmacologically relevant natural compound and support the therapeutic potential of *E. tirucalli*-derived constituents, while emphasizing the need for careful consideration of the recognized toxicological risks of this species and further clinical studies.

2.5 | Plants of the genus *Phyllanthus*

The genus *Phyllanthus* (Euphorbiaceae) comprises approximately 550–750 species distributed across tropical and subtropical regions, with nearly 200 species occurring in the Americas, particularly in Brazil and the Caribbean (Calixto et al., 1998). Several species, including *Phyllanthus niruri*, *Phyllanthus urinaria*, *Phyllanthus emblica*, *Phyllanthus amarus* and *Phyllanthus sellowianus*, are collectively known in Brazilian traditional medicine as 'quebra-pedra', and preparations as infusions or decoctions of aerial parts and roots are widely used for the management of kidney and bladder disorders, infections, diabetes and liver diseases, notably hepatitis B (see Calixto et al., 1998, for review).

Phytochemical and pharmacological studies from our research group and other researchers have identified a diverse range of bioactive constituents in *Phyllanthus* spp., including alkaloids, flavonoids, phytosterols, lignans (notably phyllanthin, hypophyllanthin and niranthin) and hydrolysable tannins such as geraniin (see Calixto et al., 1998, for review) (see Table 2). These compounds and extracts underpin a broad pharmacological profile with potential translational relevance. Several *Phyllanthus* spp. exhibit diuretic and spasmolytic effects relevant to urinary tract disorders (Calixto et al., 1998). For example, *P. sellowianus* relaxes smooth muscle in gastrointestinal and

TABLE 2 Main preclinical pharmacological effects and phytochemical structures of selected plants used in Brazilian traditional medicine: *Euphorbia tirucalli*, *Phyllanthus* spp., *Protium kleinii*/*Protium heptaphyllum* and *Trichilia catigua*.

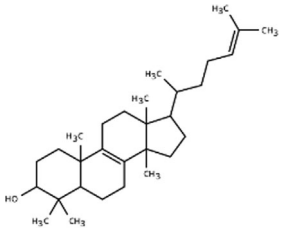
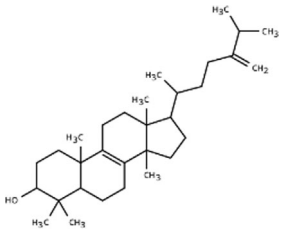
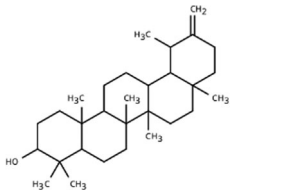
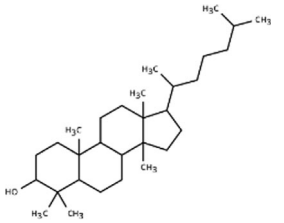
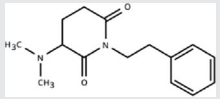
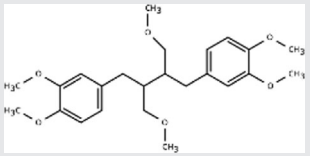
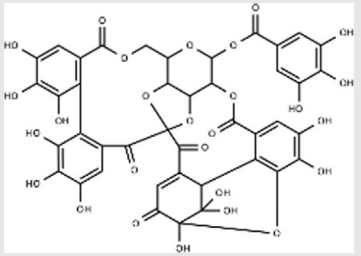
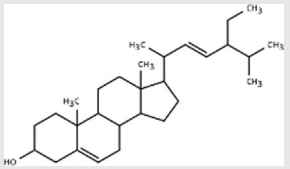
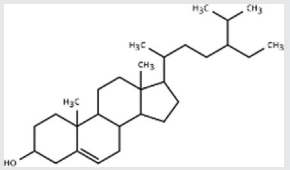
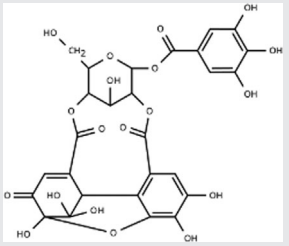
Plant species	Major compound structures	Compound/ extract used	Animal species/cell type	Disease/condition	Main results/potential mechanisms	References
E. tirucalli	Euphol	Euphol	Mice (CD1, male)	Acute colitis	↓ IL-1, CXCL1/KC, MCP-1, MIP-2, TNF-α, IL-6, NOS2, VEGF and Ki-67 expression and inhibition of activation of NF-κB	(Dutra et al., 2011)
			Mice (Swiss, C57BL/6, male) and rats (Wistar, male)	Inflammatory/ neuropathic pain	↓ MPO, TNF-α, IL-1β and IL-6 levels; prevented the up-regulation of PKCε, COX-2, NF-κB and CREB; and interaction with CB_1R and CB_2R	(Dutra et al., 2012, 2015)
	Euphorbol[a]		Mice (C57BL/6, female)	Multiple sclerosis (EAE)	↓ TNF-α, iNOS, COX-2 and LFA-1 in the CNS	(Dutra et al., 2012)
			Mice (Swiss, male)	TPA-induced skin inflammation	↓ CXCL1, MIP-2, ERK, COX-2, PKC-α and PKC-δ expression	(Passos et al., 2013)
	Taraxasterol[a]					
						
	Tirucallol[a]					
						
Phyllanthus spp.	Phyllanthimide[a]	ALK-1 (alkaloid-rich fraction)	Guinea pig (ileum, both sexes) and rat (uterus, aorta rings, both sexes)	Kidney and urinary bladder disturbances	Antispasmodic activity	(Calixto et al., 1984)
			Mice (Swiss, male)	Haemorrhagic cystitis	Attenuated CYP cystitis (↓ nociception/oedema/ haemorrhage)	(Boeira et al., 2011)
	Phyllanthin[a]					

TABLE 2 (Continued)

Plant species	Major compound structures	Compound/ extract used	Animal species/cell type	Disease/condition	Main results/potential mechanisms	References
	 Geraniin[a]	HE (callus), quercetin, GAEE and rutin				
		Hexanic extract (aerial parts) and lignan-rich fraction	Mice (Swiss, male)	Inflammatory and neuropathic pain	Inhibition of allodynia (CFA and PSNL) and oedema (CFA); ↓ MPO activity (CFA and PSNL)	(Kassuya et al., 2003)
	 Stigmasterol[a]	Extract (fruit)	In vitro: A549, HepG2, HeLa, MDA-MB-231, SK-OV3 and SW620 In vivo: Mice (ICR, male)	Various types of cancer (lung, liver, cervical, breast, ovarian and colorectal)	Inhibition of cell growth (DNA fragmentation, ↑ caspase-3/7 and ↑ Fas, in vitro), inhibition of cell invasiveness, and ↓ tumour number and volume (in vivo)	(Ngamkitidechakul et al., 2010)
	 β-Sitosterol[a]					
	 Furosin[a]					
	 Quercetin					

(Continues)

TABLE 2 (Continued)

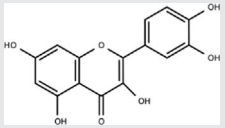
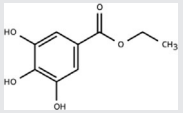
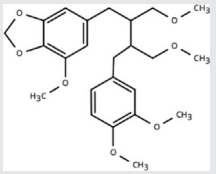
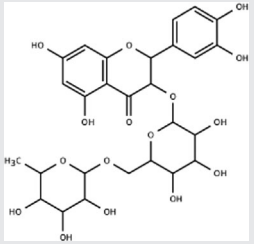
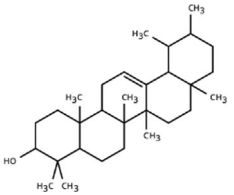
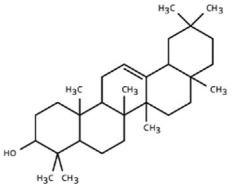
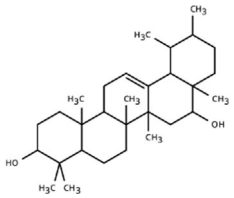
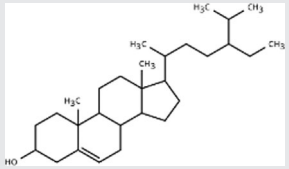
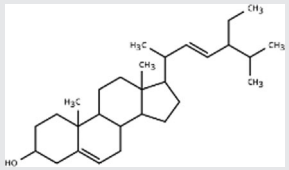
Plant species	Major compound structures	Compound/ extract used	Animal species/cell type	Disease/condition	Main results/potential mechanisms	References
	 GAEE					
	 Niranthin[a]					
	 Rutin					
						
P. kleinii/ P. heptaphyllum	α-Amyrin  β-Amyrin  Brein[a]	α-Amyrin and β-amyrin	Mice (CD1, male)	Acute colitis	↓ MPO/NAG activities, ↓ TNF-α/IL-1β/CXCL1, ↑ IL-4, ↓ adhesion molecules (ICAM-1/VCAM-1/PCAM-1), ↓ MGL-1/FAAH (↑ 2-AG/anandamide), and CB_1 blockade attenuated effects	(Matos et al., 2013, Vitor et al., 2009)
		α-Amyrin	Mice (Swiss, male)	Skin inflammation	↓ COX-2 expression, prevented IκBα degradation, p65/RelA phosphorylation and NF-κB activation	(Medeiros et al., 2007)
		α-Amyrin and β-amyrin	Mice (Swiss, male)	Inflammatory and neuropathic pain	↓ CFA/PSNL mechanical/thermal hyperalgesia + inflammation via direct CB_1/CB_2 activation, ↓ IL-1β/TNF-α/KC/IL-6 and MPO, and prevented NF-κB/ CREB/COX-2 activation	(da Silva et al., 2011)

TABLE 2 (Continued)

Plant species	Major compound structures	Compound/ extract used	Animal species/cell type	Disease/condition	Main results/potential mechanisms	References
						
T. catigua	β-Sitosterol[a] 	HE (bark)	Mice (Swiss, male) and rats (Wistar, male)	Depression	Antidepressant-like effects (forced swimming test) reversed by haloperidol/chlorpromazine, ↑ serotonin/ dopamine release and ↓ uptake in rat synaptosomes	(Campos et al., 2005)
		HE (bark)	Mice (Swiss, male)	Acute, inflammatory pain	↓ nociception (dopaminergic, Scheme 23390-reversed), ↑ apomorphine hypothermia and ↓ haloperidol catalepsy	(Viana et al., 2011)
	Stigmasterol[a] 	EAF (bark)	Rats (Wistar, male)	Cerebral ischaemia/ reperfusion	Prevention of oxidative stress (GSH/GSSG ratio, CAT and PCG) and glial cell response (GFAP immunoreactivity)	(Godinho et al., 2018)

Abbreviations: 2-AG, 2-arachidonoylglycerol; ALK-1, alkaloid-rich fraction; CAT, catalase; CB, cannabinoid receptor CB_1/CB_2; CFA, complete Freund's adjuvant; CNS, central nervous system; COX-2, cyclooxygenase 2; CREB, cAMP response element-binding protein; CXCL1, chemokine C–X–C motif ligand 1; CYP, cyclophosphamide; EAE, experimental autoimmune encephalomyelitis; EAF, ethyl acetate fraction; ERK, extracellular signal-regulated kinase; FAAH, fatty acid amide hydrolase; GAEE, gallic acid ethyl ester; GFAP, glial fibrillary acidic protein; GSH, reduced glutathione; GSSG, glutathione disulfide; HE, hydroalcoholic extract; ICAM-1, intercellular adhesion molecule-1; ICR, Institute of Cancer Research; IL-1, interleukin-1; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; KC, keratinocyte-derived chemokine; LFA-1, lymphocyte function-associated antigen 1; MCP-1, monocyte chemoattractant protein-1; MGL-1, monoacylglycerol lipase-1; MIP-2, macrophage inflammatory protein-2; MPO, myeloperoxidase; NAG, *N*-acetylglucosaminidase; NF-κB, nuclear factor-κB; NOS2, nitric oxide synthase 2; PCAM-1, platelet-endothelial cell adhesion molecule-1; PCG, protein carbonyl groups; PKC-α, protein kinase C-α; PKC-δ, protein kinase C-δ; PKCε, protein kinase C-ε; PSNL, partial sciatic nerve ligation; TNF-α, tumour necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

[a]Compound not used in isolation in the study.

vascular tissues via papaverine-like mechanisms (Calixto et al., 1984), whereas *P. urinaria* modulates urinary bladder contractility via calcium-dependent and cyclooxygenase-related pathways (Calixto et al., 1998).

Analgesic and anti-inflammatory activities have been consistently demonstrated in preclinical models. Extracts and lignan-enriched fractions from *P. amarus* reduce inflammatory and neuropathic pain (Kassuya et al., 2003), whereas flavonoids isolated from *P. niruri* attenuate cyclophosphamide-induced cystitis with efficacy comparable to Mesna (positive control) (Boeira et al., 2011), supporting their potential as adjunct therapies. Collectively, these findings identify *Phyllanthus* species as a rich source of pharmacologically active compounds with potential for translational development, particularly in inflammatory, hepatic and urological disorders (Calixto et al., 1998).

Other species of the genus, such as *P. emblica*, have demonstrated significant anti-tumour potential effects on both in vitro and in vivo models (Ngamkitidechakul et al., 2010). The aqueous fruit extract exhibited selective cytotoxicity by significantly inhibiting the growth of six different human cancer cell lines—lung (A549), liver (HepG2), cervical (HeLa), breast (MDA-MB-231), ovarian (SK-OV3) and colorectal (SW620)—while sparing normal lung fibroblasts (MRC5) (Ngamkitidechakul et al., 2010). Mechanistic investigations in the HeLa cell line revealed that the extract induces apoptosis via DNA fragmentation and marked activation of **caspase-3**, caspase-7 and caspase-8, accompanied by the up-regulation of the **Fas receptor**, indicating the involvement of the extrinsic, death receptor-mediated apoptotic pathway. Furthermore, the extract significantly attenuated the invasive capacity of metastatic breast cancer cells in in vitro invasion assays. These pharmacological properties were further validated in an in vivo model of 7,12-dimethylbenz[*a*]anthracene (DMBA)/TPA-induced skin tumourigenesis in mice, where topical application of the extract resulted in a greater than 50% reduction in both tumour number and volume. Overall, these results demonstrate the tumour-suppressive and anti-invasive potential of *P. emblica* fruit extract (Ngamkitidechakul et al., 2010).

2.6 | *Protium kleinii* and *Protium heptaphyllum*

Species of the genus *Protium* (Burseraceae), notably *P. heptaphyllum* and *P. kleinii*, are widely distributed across South America, particularly within the Amazon biome (Fine et al., 2005). These species are known in Brazilian traditional medicine as 'almécega' or 'pau-de-breu' and are valued for their aromatic oleoresins, traditionally used to treat inflammatory conditions, pain, respiratory disorders and skin injuries and as insect-repellent (Oliveira, Costa, et al., 2005; Siani et al., 1999).

Our research has focused on the pharmacological activity of extracts and isolated compounds from these species (see Table 2), with particular emphasis on the pentacyclic triterpenes present in their oleoresins. From a translational perspective, α-amyrin and β-amyrin display a pharmacological profile of considerable interest. Topical administration of α-amyrin isolated from *P. kleinii* attenuated TPA-induced ear oedema and reduced pro-inflammatory cytokine production and prostaglandin E_2 (**PGE_2**) levels (Medeiros et al., 2007). These effects were associated with inhibition of COX-2 expression and suppression of NF-κB signalling and were comparable to those of dexamethasone, without evidence of corticosteroid-like adverse effects (Medeiros et al., 2007). Moreover, in experimental models of inflammatory bowel diseases (IBDs), both triterpenoids markedly reduced TNBS- and DSS-induced colitis, an effect linked to restoration of interleukin-10 (IL-10) levels and suppression of p-NF-κB, IL-1β and COX-2 (Vitor et al., 2009).

The analgesic properties of α-amyrin and β-amyrin further reinforce their translational relevance. These compounds produced sustained antinociceptive effects in models of acute, inflammatory, visceral and neuropathic pain (da Silva et al., 2011; Medeiros et al., 2007). The underlying mechanisms involve both CB_1 and CB_2 endocannabinoid systems, inhibition of protein kinase A (PKA)- and PKC-dependent signalling pathways, suppression of NF-κB and cAMP response element-binding protein (CREB) activation, reduction of pro-inflammatory cytokines (including TNF-α, IL-1β and IL-6) and modulation of transient receptor potential vanilloid 1 (**TRPV1**) channel activity (da Silva et al., 2011; Matos et al., 2013). Notably, these effects were independent of opioid mechanisms and were not associated with sedation or motor impairment (da Silva et al., 2011).

Overall, these findings identify *Protium* species and their major triterpenes, α-amyrin and β-amyrin, as promising sources of bioactive compounds. Their multi-target mechanisms, consistent efficacy across preclinical models and favourable tolerability support further pharmacokinetic, safety and target-validation studies aimed at advancing their therapeutic potential in inflammatory and pain-related disorders.

2.7 | *Trichilia catigua*

T. catigua is a plant species native to Brazil that has long been employed in traditional medicine, particularly as a neurostimulator and aphrodisiac (Mendes & Carlini, 2007). Phytochemical investigations indicated the presence of alkaloids, lactones, phytosterols (including β-sitosterol and stigmasterol) and flavalignans, which together underpin its complex pharmacological profile (Pizzolatti et al., 2002, 2004).

Our group demonstrated that extracts of *T. catigua* produced consistent antinociceptive effects in chemical and thermal models of pain (Viana et al., 2011). These effects involve modulation of nitric oxide signalling and mechanisms that depend on opioid and dopamine pathways. Accordingly, a critical involvement of **D_1 dopamine receptors** was confirmed, suggesting a mechanistic profile distinct from that of conventional analgesics. Furthermore, *T. catigua* extract prevented apomorphine hypothermia and haloperidol-induced catalepsy (Viana et al., 2011). In parallel, *T. catigua* extract displayed consistent antidepressant-like effects in the forced swimming test (Campos et al., 2005). These effects were associated with inhibition of monoamine uptake in synaptosomes and increased release of serotonin and dopamine, indicating broad modulation of monoaminergic neurotransmission (Campos et al., 2005).

In a model of transient global cerebral ischaemia, the ethyl acetate fraction of *T. catigua* provided significant functional neuroprotection (Godinho et al., 2018). The extract demonstrated antioxidant and anti-inflammatory activity, possibly contributing to the memory protective effects after cerebral ischaemia/reperfusion (Godinho et al., 2018).

Beyond central nervous system (CNS) effects, *T. catigua* shows pharmacological activity in other systems of translational relevance. An herbal medicine containing *T. catigua* induced long-term relaxation of corpus cavernosum tissue via cAMP levels, which is consistent with its traditional use as an aphrodisiac (Antunes et al., 2001). Clinical studies conducted in healthy volunteers demonstrate that *T. catigua* extract is safe with no major adverse effects (Oliveira, Moraes, et al., 2005).

Taken together, current evidence identifies *T. catigua* as a source of bioactive compounds with a multi-target pharmacological profile, involving monoaminergic modulation, especially dopamine. The convergence of antinociceptive, antidepressant, neuroprotective, aphrodisiac and cardioprotective effects, mediated by mechanisms distinct from those of existing therapies, supports its translational relevance. However, comprehensive studies addressing pharmacokinetics, target engagement, safety and compound standardization are required to define the therapeutic potential of *T. catigua*-derived constituents are still required.

3 | IMPACT OF PHYTOMEDICINE REGULATION IN BRAZIL BY ANVISA

3.1 | Regulatory challenges and opportunities for phytomedicine development in Brazil

As already stated in this review, Brazil has a rich biodiversity, which creates opportunities for developing phytomedicines with scientific proof of efficacy and safety. To translate this potential into authorized products, Brazil relies on a regulatory framework led by Anvisa, an agency broadly comparable to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Anvisa regulation aims to ensure safety, efficacy and quality while supporting innovation and recognizing well-documented traditional knowledge associated with some few medicinal plants.

Brazilian regulation defines phytotherapeutic products as standardized plant-derived extracts obtained from one or more botanical sources, supported by scientific evidence of safety, efficacy and quality from preclinical and clinical evaluation (Anvisa, 2025). Since the late 1990s and early 2000s, Anvisa has expanded and refined this framework. Anvisa Collegiate Board Resolution (Resolução da Diretoria Colegiada [RDC]) No. 48/2004 established specific requirements for registration of herbal medicines and differentiated these products from synthetic drugs, allowing demonstration of safety, efficacy and quality through phytochemical, preclinical and clinical data and, in selected cases, through documented traditional use supported by adequate pharmaceutical quality data.

RDC No. 14/2010 further consolidated the regulatory structure by defining two categories: herbal medicines that require scientific evidence of efficacy and safety, and traditional herbal products supported by documented traditional use of at least 30 years, including at least 15 years in Brazil. RDC No. 26/2014 strengthened requirements for pharmacovigilance, quality control, extract standardization and good manufacturing practices and increased the emphasis on chemical characterization of extracts using markers, chromatographic profiles and stability studies, aligning Brazilian regulation with international guidelines from the World Health Organization and EMA. Then, the Brazilian Biodiversity Law (Law No. 13,123 of May 20, 2015, 2015) added biodiversity-related requirements by linking sanitary approval to regularization of access to genetic resources and benefit sharing, which increased legal certainty for product development.

More recently, Anvisa has introduced measures to streamline procedures without reducing technical requirements, supporting incremental innovation and reassessment of established products. This environment has supported the approval of a limited number of innovative phytomedicines derived from Brazilian biodiversity, including Acheflan® and Sintocalmy®, based on preclinical and clinical evidence (see further details in Sections 3.3 and 3.4). Overall, Anvisa regulation provides a structured pathway that integrates scientific and traditional knowledge and supports product development when developers also secure sustained financial support, manufacturing capacity and coordinated collaboration among academic groups, Brazilian pharmaceutical companies, the Ministry of Health, and the Ministry of Science, Technology and Innovation.

3.2 | Clinical research on medicinal plants in Brazil: Challenges and opportunities for translation

As illustrated in Section 2.2 (Figure 1), Brazilian contributions to indexed journals in the field of medicinal plants are prominent at the international level, underscoring the country's scientific relevance in this domain. Nevertheless, a considerable proportion of this research, largely conducted within academic institutions, remains insufficiently integrated with industrial partners. Furthermore, regulatory considerations are often not incorporated at early stages of research and development, limiting the progression of promising findings into clinical trials in humans, a critical step for regulatory approval and therapeutic use.

Given the longstanding and widespread use of medicinal plants in Brazil, there is increasing emphasis on generating robust scientific evidence to support their rational use. Efforts have focused mainly on the identification and characterization of bioactive constituents, demonstration of efficacy and elucidation of pharmacological mechanisms through well-designed preclinical and clinical studies. This has facilitated the integration of traditional knowledge with modern pharmacological science and has stimulated innovation in plant-derived therapeutics.

Despite these advances, the translation of Brazil's biodiversity into innovative medicines remains limited. Contributing factors

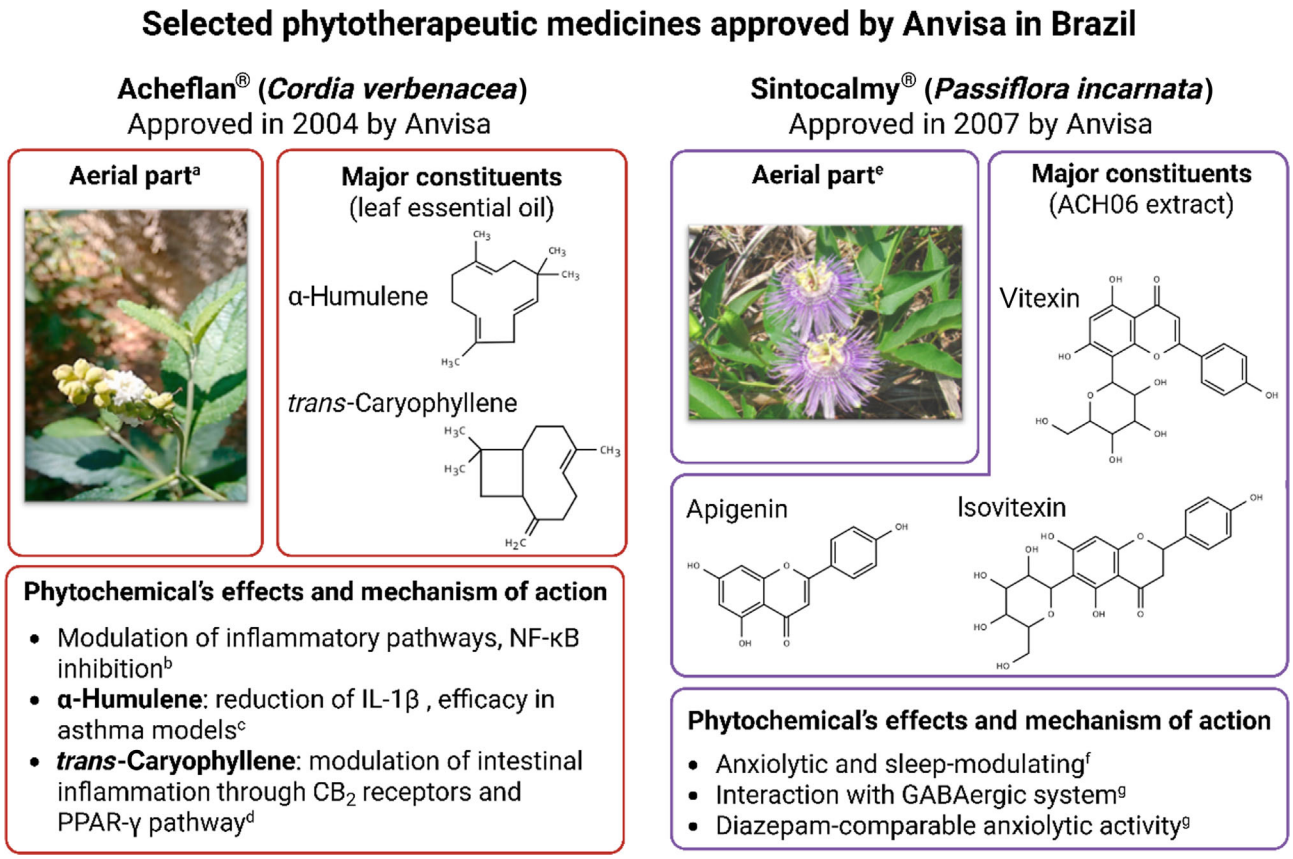


FIGURE 3 Acheflan® and Sintocalmy® main active compounds and their pharmacological effects. [a]Martim et al. (2021). [b]Medeiros et al. (2007). [c]Rogerio et al. (2009). [d]Bento et al. (2011). [e]Guseinov et al. (2019). [f]McGregor et al. (2008). [g]Grundmann et al. (2008).

include historical regulatory constraints on access to genetic resources (in place until 2015), which restricted research and development activities in both academia and industry. In addition, the domestic pharmaceutical sector has traditionally prioritized generic drug production over investment in innovative R&D. The lack of sustained public policies promoting collaboration between academia and industry has further hindered translational progress.

Regulatory challenges also remain a key barrier, particularly with respect to the efficiency of clinical trial authorization and the approval of new medicines by the FDA-like Brazilian agency Anvisa. Strengthening regulatory frameworks and improving process efficiency are essential to accelerate the development pipeline. In this context, aligning scientific, industrial and regulatory strategies will be critical to unlocking the full therapeutic potential of Brazil's biodiversity.

3.3 | Development of the phytomedicine Acheflan® from the Brazilian plant *C. verbenacea*

C. verbenacea D.C. (formerly classified as *Cordia curassavica*) is a Brazilian native species of the Boraginaceae family, widely distributed along the south-eastern coast. Its aerial parts exhibit a strong, persistent aroma and are traditionally used in Brazilian folk medicine as alcoholic extracts, decoctions and infusions, with reported anti-ulcer, antimicrobial, anti-inflammatory, anti-rheumatic, analgesic and tonic properties.

Phytochemical studies of ethanolic leaf extracts indicate a diverse composition, including tannins, flavonoids and essential oils (Sertié et al., 1988, 1991). The essential oil is mainly composed of monoterpenes and sesquiterpenes, with constituents such as α-pinene, *trans*-caryophyllene and alloaromadendrene (De Carvalho et al., 2004). Within the regulatory pathway described in Section 3.1, Acheflan® illustrates how Brazil can translate traditional use and academic pharmacology into a registered phytomedicine when industry commits to development (Figure 3). Acheflan® is a topical phytomedicine developed from the essential oil of *C. verbenacea*, a Brazilian species traditionally used for pain and inflammatory conditions. This case supports a central premise of this review: Product development requires coordinated selection of a relevant species, standardization of the active preparation, long-term stability of the major constituents, well-conducted and reproducible preclinical pharmacology studies, and well-conducted clinical trials to confirm the safety and efficacy under a defined regulatory framework. In 1998, Aché Laboratory redirected its strategy towards innovation based on national biodiversity and established a programme to prioritize species with consistent traditional use and pharmacological plausibility. To this end, a group of researchers and consultants was assembled with the task of selecting Brazilian plants with a strong tradition of medicinal use and

demonstrable pharmacological potential. Among the species initially considered, *C. verbenacea*, popularly known as 'erva-baleeira' or 'maria-milagrosa', stood out. In addition to its frequent use by local populations to treat pain and inflammation, Aché Laboratory had already conducted preliminary studies on this plant in partnership with the University of São Paulo, without conclusive results (Sertié et al., 1988, 1991, 2005).

Given the limitations of earlier studies using plant extracts, the group decided to adopt a new strategy: to investigate the essential oil extracted from the leaves of *C. verbenacea*; this approach proved decisive. Chemical analysis of the oil led to the identification of several compounds, with particular emphasis on two sesquiterpenes: α-humulene and *trans*-caryophyllene (or β-caryophyllene), which demonstrated marked anti-inflammatory and analgesic effects in experimental models administered topically and systemically (Bento et al., 2011; Fernandes et al., 2007; Medeiros et al., 2007; Passos et al., 2007; Rogerio et al., 2009; Segat et al., 2017).

Building on this background, the partnership between academic researchers and Aché Laboratory was consolidated in the early 2000s, with a specific focus on the plant's essential oil. Preclinical studies conducted by our research group demonstrated that this oil consistently inhibited oedema induced by various inflammatory agents, including carrageenan, BK, histamine and substance P. Moreover, it reduced neutrophil migration and modulated allergic inflammatory responses, including in models of ovalbumin-induced asthma. These effects were mainly associated with reductions in pro-inflammatory cytokines, such as TNF-α, without direct inhibition of the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, which are common targets of traditional anti-inflammatory drugs.

Mechanistic studies revealed that α-humulene and *trans*-caryophyllene act by modulating key inflammatory pathways, including inhibition of the transcription factor NF-κB. α-Humulene exhibited additional relevant effects, such as reduction of IL-1β levels and down-regulation of receptors involved in inflammation, and marked efficacy in models of allergic asthma (Fernandes et al., 2007; Medeiros et al., 2007; Passos et al., 2007; Rogerio et al., 2009). Alongside, *trans*-caryophyllene demonstrated a central role in modulating intestinal inflammation in an experimental model of DSS-induced colitis, with effects mediated by cannabinoid CB_2 receptors and the peroxisome proliferator-activated receptor-γ (**PPAR-γ**) pathway, suggesting therapeutic potential for IBD (Bento et al., 2011). Furthermore, *trans*-caryophyllene exhibited an anti-allodynic effect in a paclitaxel-induced peripheral neuropathy model, associated with up-regulation of CB_2 receptors and its transcripts (Segat et al., 2017).

Preventive or therapeutic treatments with α-humulene orally or by aerosol exhibited marked anti-inflammatory properties in a murine model of airways allergic inflammation, an effect mediated by the reduction of inflammatory mediators, inhibition of NF-κB and activator protein 1 (AP-1) activation, expression of P-selectin and increased mucus secretion in the lung (Rogerio et al., 2009). Furthermore, both compounds exhibited long-lasting analgesic effects in different pain models, including inflammatory, neuropathic and post-surgical pain.

Pharmacokinetic studies demonstrated that α-humulene has relatively rapid absorption following oral and topical administration, reaching relevant concentrations in target tissues (Chaves et al., 2008). Collectively, these findings helped to explain the clinical efficacy observed with Acheflan® topical formulations. In parallel, toxicological studies in rodents and dogs indicated a high safety profile, even after prolonged administration. Based on this robust body of preclinical evidence, phase I, II and III clinical studies were conducted, confirming the safety and efficacy of *C. verbenacea* essential oil as a topical analgesic and anti-inflammatory agent. In 2004, the product was approved by the Brazilian regulatory agency Anvisa and launched on the Brazilian market in 2005 under the name Acheflan® (Aché Laboratórios Farmacêuticos S.A., 2025a). Subsequently, in 2007, a spray formulation was introduced, further expanding its clinical acceptance.

Since then, Acheflan® has become the most widely prescribed topical medicine in Brazil for the treatment of pain and inflammation, currently accounting for approximately 50% of prescriptions in this category. Acheflan® is also exported to several countries across different continents. Cumulative sales since its launch represent significant economic value, consolidating the product as a commercial and scientific success. Therefore, Acheflan® represents a rare example of pharmaceutical innovation based on Brazilian biodiversity and demonstrates that rigorous science, sustained industrial investment and supportive industrial policy can translate a native species into a regulated therapeutic product with clinical and commercial uptake in Brazil.

3.4 | Development of the phytomedicine Sintocalmy® from *P. incarnata*

Following the development pathway described for Acheflan® and within the regulatory framework of Anvisa, Sintocalmy® provides an example of incremental innovation based on standardization and repositioning of an established herbal medicine for CNS indications (Figure 3). *P. incarnata* has a long history of use for anxiety and insomnia, and several international monographs and pharmacopoeias describe its preparations for these indications (British Herbal Medicine Association [BHMA], 1983; EMA, 2014).

Around 2006, after the commercial and clinical consolidation of Acheflan®, Aché Laboratory decided to invest in the development of a phytomedicine aimed at the treatment of CNS-related disorders. This initiative was motivated by the high incidence of anxiety and insomnia and the widespread use of benzodiazepines, which, although effective, are associated with important adverse effects (i.e., sedation and dependence). The search for Brazilian plants with a strong tradition of popular use for these indications proved to be limited, particularly when large-scale cultivation was required. As an alternative, a strategy of technological repositioning was adopted, focusing on an already well-established herbal medicine derived from *P. incarnata*.

P. incarnata belongs to the family Passifloraceae and is widely distributed in temperate and tropical regions. Its hydroalcoholic extract, obtained mainly from the leaves, has been traditionally used in several

countries for the treatment of anxiety and insomnia. The species is included in numerous international pharmacopoeias and monographs, including those of France (Agence nationale de sécurité du médicament et des produits de santé [ANSM], 2007) and Switzerland (Swissmedic, 2006) and in EMA documents (EMA, 2014). Preclinical studies conducted by our research group have demonstrated that the extract exhibits anxiolytic and sleep-modulating effects in animal models, which are mainly attributed to the flavonoids present in the plant, such as vitexin, isovitexin and apigenin, known to interact with the GABAergic system (De Oliveira et al., 2020; Elsas et al., 2010).

The innovative strategy adopted consisted of an extensive phytochemical investigation aimed at removing alkaloids potentially associated with adverse effects while concentrating the flavonoid fraction. The resulting extract, designated ACH06, was standardized to contain 42 mg (7%) of total flavonoids expressed as vitexin. Non-clinical studies conducted by our group at the Federal University of Santa Catarina demonstrated that ACH06 exhibited anxiolytic activity comparable to that of diazepam, with a favourable safety (toxicological) profile.

On the basis of these findings, a phase III clinical trial was conducted comparing ACH06 with diazepam in patients with anxiety and sleep disorders. The phytomedicine showed clinical efficacy similar to that of the reference drug. As a result, the product was approved by Anvisa under the name Sintocalmy® (Aché Laboratórios Farmacêuticos S.A., 2025b), with indications for irritability, nervous agitation, insomnia and anxiety disorders. Launched in 2010, Sintocalmy® achieved wide medical acceptance and has since become one of the most frequently prescribed phytomedicines in Brazil.

4 | POTENTIAL PHYTOTHERAPEUTIC MEDICINES CURRENTLY IN DEVELOPMENT BY OUR RESEARCH GROUP

4.1 | Non-clinical efficacy and regulatory safety assessment of a standardized extract of *Ilex paraguariensis* for metabolic disorders

I. paraguariensis (yerba mate) is widely consumed in South America and has long been associated with health-promoting effects. Accumulating preclinical and limited observational clinical evidence indicates beneficial actions of *I. paraguariensis* extracts in metabolic disorders, including obesity, dyslipidaemia and type 2 diabetes mellitus (Bastos et al., 2007; Gambero & Ribeiro, 2015; Lima et al., 2014; Pereira et al., 2012; Pimentel et al., 2013; Valenca et al., 2022; see José et al., 2023, for review). However, despite extensive traditional use, no fully standardized extract had previously undergone a comprehensive non-clinical development programme compliant with regulatory requirements for the development of innovative phytotherapeutic medicine.

To address this gap, our group generated a quite complete non-clinical dossier in accordance with guidelines from Anvisa and other regulatory agencies, aiming to support the clinical development of a phytomedicine (Tolouei et al., 2025). Leaves and young branches of *I. paraguariensis* were botanically authenticated and extracted using hot aqueous extraction, selected based on yield, scalability and regulatory suitability. The resulting extract (yield ~17%) was chemically characterized by ultra-performance liquid chromatography–mass spectrometry (UPLC–MS), identifying caffeine, theophylline, theobromine, rutin and caffeoylquinic acids as major constituents (Tolouei et al., 2025).

A single spray-dried batch (about 4 kg), produced under industrial conditions, was used throughout the programme. Quantitative analyses confirmed consistent levels of alkaloids, phenolic acids and flavonoids, and long-term stability studies demonstrated chemical integrity for at least 30 months. Regulatory-relevant drug–enzyme interaction studies showed no interaction on CYP3A4 activity in vivo, as assessed by midazolam pharmacokinetics in rats, indicating a low risk of clinically significant herb–drug interactions (Tolouei et al., 2025).

Pharmacokinetic studies performed in both mice and rats demonstrated rapid oral absorption and sustained systemic exposure of the principal alkaloids caffeine, theophylline and theobromine following acute and repeated dosing. Efficacy was evaluated in multiple in vivo validated models relevant to metabolic disease, including diet-induced obesity, non-alcoholic hepatic steatosis, streptozotocin-induced type 2 diabetes mellitus and diabetes-associated hypertension. Therapeutic administration of the extract reduced body weight gain, food intake and glucose intolerance, with efficacy comparable to liraglutide. Treatment normalized plasma glucose, insulin, leptin and cholesterol levels; reduced adipose and liver mass; and significantly lowered circulating pro-inflammatory cytokines (Tolouei et al., 2025).

Histological and molecular analyses demonstrated the modulation of several relevant genes, protection against hepatic steatosis, reduced lipid accumulation and down-regulation of fibrosis-related and inflammasome-associated genes. Mechanistic investigations revealed coordinated modulation of pathways involved in lipid metabolism, satiety and inflammation across adipose tissue, liver and hypothalamus. Comprehensive Good Laboratory Practice (GLP)-compliant safety studies showed no genotoxicity, no relevant toxicity in maximum tolerated dose or 90-day repeated-dose studies in rats, and no adverse effects in CNS or cardiovascular safety pharmacology assays (Tolouei et al., 2025).

In conclusion, this standardized aqueous extract of *I. paraguariensis* demonstrates robust efficacy and a favourable regulatory safety profile across multiple preclinical models of metabolic disease. Completion of ongoing non-rodent toxicity studies will enable regulatory submission to Anvisa and FDA, supporting first-in-human clinical development.

4.2 | Non-clinical efficacy and regulatory safety assessment of a standardized extract of *Justicia pectoralis* for respiratory inflammation

J. pectoralis Jacq. (Acanthaceae) is a perennial herb native to Brazil and other Latin American countries, traditionally used to treat respiratory disorders (Leal et al., 2017; Nunes et al., 2018). Its leaves are

commonly prepared as infusions and valued for their expectorant properties (Leal et al., 2017; Rosa Júnior et al., 2024). The species is included in RENISUS and listed in the Brazilian Pharmacopoeia, where it is indicated as an expectorant (Anvisa, 2021).

Preclinical studies with different extracts report multiple pharmacological activities, including anti-inflammatory, antioxidant, sedative, anxiolytic, estrogenic and gastroprotective effects (Rosa Júnior et al., 2024; Timalsina et al., 2021; Wieczfinska et al., 2020). Extracts also show antimicrobial activity against clinically relevant pathogens such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella enteritidis* and *Escherichia coli* (Nunes et al., 2018; Oliveira et al., 2023). Phytochemical studies indicate a diverse profile rich in coumarins, flavonoids and alkaloids, which likely underpin its anti-inflammatory, bronchodilatory and expectorant effects (Moura et al., 2017; Nunes et al., 2018).

Recently our group published a robust preclinical development using TI-138, a fully standardized *J. pectoralis* extract (Tolouei et al., 2026). The extract was chemically characterized by liquid chromatography–tandem mass spectrometry (LC–MS/MS), and stability studies demonstrated a consistent phytochemical profile for more than 28 months. Pharmacokinetic evaluation in rats showed rapid oral absorption ($T_{max} = 0.25$ h), with sustained peak plasma concentrations of its principal markers, coumarin (~1.5 μg·ml^{-1}) and *o*-coumaric acid (~2.0 μg·ml^{-1}). Importantly, interaction studies revealed no significant effects on CYP3A4 activity, suggesting a low potential for clinically relevant herb–drug interactions.

The therapeutic efficacy of orally administered TI-138 was demonstrated across three distinct in vivo models of respiratory disease. The extract produced marked expectorant and antitussive effects and significantly attenuated airway inflammation and tissue remodelling in experimental asthma. Mechanistic analyses, including polymerase chain reaction (PCR) arrays, quantitative reverse transcription PCR (RT-qPCR) and enzyme-linked immunosorbent assay (ELISA), indicated that TI-138 exerts its effects through modulation of immune-regulatory pathways. Treatment suppressed a broad panel of pro-inflammatory genes, including interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-13 (IL-13), interleukin-17a (IL-17a) and TNF-α, and down-regulated key chemokines and receptors (**CCL5**, CCR4, CD4 and CD28) to levels below those observed in healthy controls. At the protein level, these transcriptional changes were associated with a marked reduction in pulmonary IgE and key inflammatory cytokines, including IL-5, IL-13 and TNF-α (Tolouei et al., 2026).

In addition to its efficacy, the formulation underwent an extensive battery of safety pharmacology and toxicological assessments conducted under GLP conditions. TI-138 showed no evidence of genotoxicity and exhibited a favourable safety profile in both acute and repeated-dose toxicity studies. Furthermore, evaluations of the CNS, cardiovascular system and respiratory system revealed no adverse off-target effects at therapeutically relevant doses (Tolouei et al., 2026).

Taken together, the pharmacological, mechanistic and safety data generated for the standardized TI-138 extract provide strong support for the traditional use of *J. pectoralis*. By meeting stringent non-clinical regulatory requirements, these findings establish a solid foundation for the progression of this candidate into clinical trials for the treatment of inflammatory respiratory diseases (Tolouei et al., 2026).

4.3 | Non-clinical efficacy and regulatory safety assessment of a standardized extract of *Apuleia ferrea* for chronic inflammatory bowel diseases (IBDs)

Libidibia ferrea (Mart. ex Tul.) L.P. Queiroz (syn. *Caesalpinia ferrea* and *A. ferrea*), commonly known as 'jucá' or Brazilian ironwood, is a native and endemic plant from Brazil and widely used in traditional medicine for treating wounds, inflammation, respiratory and gastrointestinal disorders, diabetes and rheumatism, typically as infusions or topical preparations. Preclinical studies have demonstrated significant wound-healing, anti-inflammatory and antimicrobial activities, with evidence from in vitro assays and animal models, including enhanced dermal repair in rodents, goats and dogs. Phytochemical analyses reveal a complex composition rich in polyphenols (e.g., tannins), flavonoids, saponins and terpenoids, which are considered responsible for its biological effects (Carvalho et al., 1996; Falcão et al., 2019; see Almeida et al., 2021; Macêdo et al., 2020, for review).

Our group evaluated the preclinical efficacy, mechanisms of action and GLP safety preclinical studies of a standardized extract of *A. ferrea* (Test Item 118), aiming to support the regulatory development of a phytomedicine for management of chronic IBDs, particularly ulcerative colitis and Crohn's disease (Calixto, 2026). The programme was conducted in line with national and international regulatory guidelines and integrated chemical characterization, long-term stability assessment, pharmacokinetics, evaluation of drug–enzyme interactions, demonstration of in vitro and in vivo proof of concept (efficacy) in validated experimental models, molecular studies to access the mechanisms of action and a comprehensive regulatory battery of preclinical safety studies.

Plant material was collected in the herbarium of Universidade de Ribeirão Preto (UNAERP), state of São Paulo; botanically authenticated; and deposited in a recognized herbarium. Following comparative extraction studies, a hydroalcoholic extract (50% v/v ethanol) prepared from the aerial parts was selected based on extraction efficiency, scalability and regulatory suitability. In collaboration with the Centroflora company, a single 4-kg spray-dried batch was produced and used throughout the programme. Chemical characterization using advanced UPLC–MS chromatographic techniques identified flavonoids, phenolic acids and tannins as the predominant bioactive classes. Major constituents included gallic acid, epicatechin, quercetin, naringenin, hispidulin, caffeic acid, galloylquinic acid derivatives and gallotannins. The extract showed high chemical and biological stability for at least 14 months.

Pharmacokinetic studies demonstrated low systemic exposure of the principal phenolic compounds following oral administration, with plasma concentrations below the limit of quantification after both acute and repeated dosing. This pharmacokinetic profile strongly suggests that the therapeutic effects are predominantly mediated by local

action within the intestinal lumen and mucosa or through intestinal microbiota, a highly desirable feature for the treatment of IBD. Consistent with this, the extract did not significantly interfere with cytochrome P450 3A4 activity, indicating a low potential for clinically relevant herb–drug interactions.

Preclinical efficacy was demonstrated in both in vitro and in vivo models. In intestinal epithelial cells stimulated with lipopolysaccharide, the extract significantly reduced interleukin-8 (IL-8) release, indicating direct suppression of pro-inflammatory signalling at the epithelial level. In murine DSS- and TNBS-induced colitis models, oral treatment attenuated body weight loss, disease activity index, colon shortening and histopathological damage, accompanied by marked reductions in key pro-inflammatory cytokines, including IL-6, TNF-α, interleukin-17 (IL-17) and interferon-γ (IFN-γ) (Calixto, 2026).

Mechanistic investigations provided important insights into the molecular basis of these effects. Transcriptomic analyses using PCR arrays and RT-qPCR revealed coordinated down-regulation of genes associated with inflammasome activation, cytokine signalling and tissue injury, alongside up-regulation of pathways related to cytoprotection, epithelial regeneration and metabolic homeostasis. Notably, modulation of genes involved in immune regulation (e.g., IL-6, TNF-α and signal transducer and activator of transcription [**STAT**]), cell cycle control and proliferation (proliferating cell nuclear antigen [PENA] and cyclin-dependent kinase inhibitor 2A [CDKN2A]), tissue remodelling (T-cell immunoglobulin and mucin domain 1 [TIM1]), oxidative stress responses (heme oxygenase 1 [HMOX1] and iNOS) and epithelial repair (epidermal growth factor receptor [**EGFR**], prominin-1 [PROM1] and catenin beta-1 [CTNB1]) was observed. Immunohistochemical analyses corroborated these findings, demonstrating reduced inflammatory infiltrates and enhanced markers of mucosal repair (Calixto, 2026).

The gastroprotective effects of the extract were further confirmed in a chronic acetic acid-induced gastric ulcer model in rats, in which treatment significantly reduced lesion area and volume, supporting a broader role in mucosal protection and tissue healing. Comprehensive GLP-compliant non-clinical safety studies conducted in rodents demonstrated no mutagenic or genotoxic effects, no toxicity in maximum tolerated dose or 90-day repeated-dose oral toxicity studies, and no adverse effects on the CNS, cardiovascular system or respiratory system.

In conclusion, the standardized extract of *A. ferrea* exhibits a robust anti-inflammatory and mucosal-protective profile mediated by multi-target modulation of inflammatory, immune and regenerative pathways, combined with a favourable preclinical safety profile. These findings provide strong mechanistic and regulatory support for continued development and submission to health authorities to enable clinical evaluation in patients with IBDs to confirm its clinical efficacy.

5 | CONCLUDING REMARKS AND FUTURE DIRECTION

Despite its extraordinary biodiversity and the extensive body of published chemical and biological research on Brazilian plants in the last decades, Brazil still lacks a coherent, durable national long-term strategy to translate its biological resources into sustained medical innovation products that effectively benefit its population. Persistent regulatory constraints; the limited interest of domestic pharmaceutical companies in innovation; difficulties in conducting clinical trials—particularly early-phase (phase I) studies; and the increasing complexity, bureaucracy and scope of regulatory oversight Anvisa have collectively hindered scientific progress and technological development.

Although the enactment of the Brazilian Biodiversity Law (Law No. 13,123 of May 20, 2015, 2015) represented an important regulatory milestone, critical aspects of its implementation remain insufficiently defined. Ongoing uncertainties regarding genetic information, associated traditional knowledge, prior informed consent and access to biological materials continue to discourage research and innovation. Without urgent regulatory clarification and greater legal certainty, the scientific and therapeutic potential of Brazil's biodiversity will remain largely underexploited.

These structural limitations are clearly reflected in the current market landscape. Among the 20 leading phytotherapeutic products commercialized in Brazil in 2024 (see Table 1), only three were developed domestically, all of which involved partnerships with our research group for the conduct of preclinical studies. To date, only two phytotherapeutic medicines originating from Brazilian native biodiversity, *C. verbenacea* and *M. glomerata*, have received regulatory approval by Anvisa for human use and remain commercially available. Moreover, the phytomedicine sector has continued to decline, currently representing about 2% of the national pharmaceutical market, compared with around 4%–5% in 2010.

Finally, reflecting on more than four decades of research and innovation activities conducted by our research group on Brazilian medicinal plants, we recognize that meaningful scientific advances have been achieved, albeit with limited translation into innovative products. The restricted engagement of the national pharmaceutical industry in innovation-driven drug development, combined with the lack of sustained governmental and political support for basic research and long-term innovation policies, remains a major structural bottleneck. This persistent lack of commitment continues to undermine Brazil's capacity to develop innovative medicines domestically and to strategically capitalize on the exceptional value of its rich biodiversity. Nevertheless, considerable efforts are still required to reach this goal.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/26 (Alexander, Cidlowski et al., 2025; Alexander, Davenport et al., 2025; Alexander, Fabbro, Gibb, et al., 2025; Alexander, Fabbro, Peach, et al., 2025; Alexander, Gibb et al., 2025; Alexander, Striessnig et al., 2025).

AUTHOR CONTRIBUTIONS

João Vitor A. Hoepers: Writing—original draft; writing—review and editing. **Letícia C. N. Takasumi:** Writing—original draft; writing—review and editing. **João B. Calixto:** Conceptualization; supervision; writing—original draft; writing—review and editing.

ACKNOWLEDGEMENTS

We thank Dr Guilherme Pasetto Fadanni from Aché Laboratory for providing information on the Brazilian phytomedicine market. The articles from our group cited in this review article were supported by the Brazilian National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico [CNPq]), Funding Authority for Studies and Projects (Financiadora de Estudos e Projetos [FINEP]), the Ministry of Health (Ministério da Saúde), the Ministry of Science, Technology and Innovation (Ministério da Ciência, Tecnologia e Inovação), Coordination for the Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior [CAPES]) and the Research Support Foundation of the State of Santa Catarina (Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina [FAPESC]), Brazil. João Vitor A. Hoepers is a PhD student, supported by CAPES, and Letícia C. N. Takasumi is a postdoctoral student supported by CNPq. We thank the Centroflora partnership for preparing the spray dryer single-batch standardized extracts of some medicinal plants studied by our group.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

João Vitor A. Hoepers https://orcid.org/0000-0002-0017-6327
Letícia C. N. Takasumi https://orcid.org/0009-0009-5014-2975
João B. Calixto https://orcid.org/0000-0003-4041-7153

REFERENCES

Aché Laboratórios Farmacêuticos S.A. (2025a). Acheflan (*Cordia verbenacea* DC.) (Bula Do Profissional Registro: 105730341). Aché Laboratórios Farmacêuticos S.A. https://consultas.anvisa.gov.br/#/bulario/detalhe/385200?numeroRegistro=105730341

Aché Laboratórios Farmacêuticos S.A. (2025b). Sintocalmy (*Passiflora incarnata* L.) (Bula Do Profissional Registro: 105730368). Aché Laboratórios Farmacêuticos S.A. https://consultas.anvisa.gov.br/#/bulario/detalhe/460014?numeroRegistro=105730368

Agence nationale de sécurité du médicament et des produits de santé. (2007). *Pharmacopée française* (11e édition ed.). ANSM.

Alexander, S. P. H., Cidlowski, J. A., Gibb, A. J., Kelly, E., Mathie, A. A., Peach, C. J., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Coons, L., Fuller, P. J., Korach, K. S., McDonell, D. P., Oakley, R., Radi, S., Safi, R., … Young, M. J. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Nuclear hormone receptors. *British Journal of Pharmacology*, *182*(Suppl 1), S242–S258. https://doi.org/10.1111/bph.70232

Alexander, S. P. H., Davenport, A. P., Kelly, E., Gibb, A. J., Mathie, A. A., Peach, C. J., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Abbracchio, M. P., Abraham, G. R., Agoulnik, A., Alexander, W., Al-hosaini, K., Bäck, M., Baker, J. G., … Zaidman, N. (2025). The Concise Guide to PHARMACOLOGY 2025/26: G protein-coupled receptors. *British Journal of Pharmacology*, *182*(Suppl 1), S24–S151. https://doi.org/10.1111/bph.70230

Alexander, S. P. H., Fabbro, D., Gibb, A. J., Kelly, E., Mathie, A. A., Peach, C. J., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Annett, S., Boison, D., Burns, K. E., Dessauer, C., Gertsch, J., Helsby, N. A., Izzo, A. A., … Wong, S. S. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Enzymes. *British Journal of Pharmacology*, *182*(Suppl 1), S307–S403. https://doi.org/10.1111/bph.70234

Alexander, S. P. H., Fabbro, D., Peach, C. J., Gibb, A. J., Kelly, E., Mathie, A. A., Veale, E. L., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Beuve, A., Brouckaert, P., Bryant, C., Burnett, J. C., Farndale, R. W., Friebe, A., Garthwaite, J., … Waldman, S. A. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Catalytic receptors. *British Journal of Pharmacology*, *182*-(Suppl 1), S259–S306. https://doi.org/10.1111/bph.70233

Alexander, S. P. H., Gibb, A. J., Kelly, E., Mathie, A. A., Peach, C. J., Veale, E. L., Cidlowski, J. A., Davenport, A. P., Fabbro, D., Spedding, M., Striessnig, J., Armstrong, J. F., Buneman, O. P., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Ahlers-Dannen, K. E., Alqinyah, M., … Zolghadri, Y. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Introduction and Other Protein Targets. *British Journal of Pharmacology*, *182*(Suppl 1), S1–S23. https://doi.org/10.1111/bph.70229

Alexander, S. P. H., Striessnig, J., Gibb, A. J., Mathie, A. A., Veale, E. L., Kelly, E., Peach, C. J., Armstrong, J. F., Faccenda, E., Harding, S. D., Southan, C., Davies, J. A., Aldrich, R. W., Attali, B., Baggetta, A. M., Becirovic, E., Beech, D. J., Biel, M., Bill, R. M., … Zhu, M. (2025). The Concise Guide to PHARMACOLOGY 2025/26: Ion channels. *British Journal of Pharmacology*, *182*(Suppl 1), S152–S241. https://doi.org/10.1111/bph.70231

Almeida, N. C. O. S., Silva, F. R. P., Carneiro, A. L. B., Lima, E. S., Barcellos, J. F. M., & Furtado, S. C. (2021). *Libidibia ferrea* (jucá) anti-inflammatory action: A systematic review of *in vivo* and *in vitro* studies. *PLoS ONE*, *16*(11), e0259545. https://doi.org/10.1371/journal.pone.0259545

Antunes, E., Gordo, W. M., De Oliveira, J. F., Teixeira, C. E., Hyslop, S., & De Nucci, G. (2001). The relaxation of isolated rabbit corpus cavernosum by the herbal medicine Catuama® and its constituents. *Phytotherapy Research*, *15*(5), 416–421. https://doi.org/10.1002/ptr.861

Anvisa. 2014. Monografia da espécie *Mikania glomerata* (guaco) [Monografia de planta medicinal/monografia técnica]. Ministério da Saúde, Anvisa. https://www.gov.br/saude/pt-br/composicao/sectics/plantas-medicinais-e-fitoterapicos/ppnpmf/arquivos/2016/MonografiaMikania.pdf

Anvisa. (2021). Formulário de fitoterápicos da farmacopeia brasileira, 2ª Edição [Monografia]. Anvisa. https://bibliotecadigital.anvisa.gov.br/jspui/bitstream/anvisa/836/1/FORMULARIO%20DE%20FITOTERAPICOS.pdf

Anvisa. (2025). Anvisa aprova novo marco para medicamentos fitoterápicos no Brasil. https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2025/anvisa-aprova-novo-marco-para-medicamentos-fitoterapicos-no-brasil

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., & Supuran, C. T. (2021). Natural products in drug discovery: Advances and opportunities. *Nature Reviews Drug Discovery*, *20*(3), 200–216. https://doi.org/10.1038/s41573-020-00114-z

Atanasov, A. G., Waltenberger, B., Pferschy-Wenzig, E.-M., Linder, T., Wawrosch, C., Uhrin, P., Temml, V., Wang, L., Schwaiger, S., Heiss, E. H., Rollinger, J. M., Schuster, D., Breuss, J. M., Bochkov, V., Mihovilovic, M. D., Kopp, B., Bauer, R., Dirsch, V. M., & Stuppner, H. (2015). Discovery and resupply of pharmacologically active plant-derived natural products: A review. *Biotechnology Advances*, *33*(8), 1582–1614. https://doi.org/10.1016/j.biotechadv.2015.08.001

Bastos, D. H., Saldanha, L. A., Catharino, R. R., Sawaya, A., Cunha, I. B., Carvalho, P. O., & Eberlin, M. N. (2007). Phenolic antioxidants

identified by ESI-MS from yerba maté (*Ilex paraguariensis*) and green tea (*Camelia sinensis*) extracts. *Molecules*, *12*(3), 423–432. https://doi.org/10.3390/12030423

Bento, A. F., Marcon, R., Dutra, R. C., Claudino, R. F., Cola, M., Leite, D. F. P., & Calixto, J. B. (2011). β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPARγ pathway. *The American Journal of Pathology*, *178*(3), 1153–1166. https://doi.org/10.1016/j.ajpath.2010.11.052

Betancur-Galvis, L. A., Morales, G. E., Forero, J. E., & Roldan, J. (2002). Cytotoxic and antiviral activities of Colombian medicinal plant extracts of the *Euphorbia* genus. *Memórias Do Instituto Oswaldo Cruz*, *97*, 541–546. https://doi.org/10.1590/S0074-02762002000400017

Biondo, R., Pereira, A. M. S., Marcussi, S., Pereira, P. S., França, S. C., & Soares, A. M. (2003). Inhibition of enzymatic and pharmacological activities of some snake venoms and toxins by *Mandevilla velutina* (Apocynaceae) aqueous extract. *Biochimie*, *85*(10), 1017–1025. https://doi.org/10.1016/s0300-9084(03)00138-x

Boeira, V. T., Leite, C. E., Santos, A. A. Jr., Edelweiss, M. I., Calixto, J. B., Campos, M. M., & Morrone, F. B. (2011). Effects of the hydroalcoholic extract of *Phyllanthus niruri* and its isolated compounds on cyclophosphamide-induced hemorrhagic cystitis in mouse. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *384*(3), 265–275. https://doi.org/10.1007/s00210-011-0668-0

British Herbal Medicine Association. (1983). *British herbal pharmacopoeia* (1st ed.). British Herbal Medicine Association.

Calixto, J. B. (2019). The role of natural products in modern drug discovery. *Anais da Academia Brasileira de Ciências*, *91*(Suppl 3), e20190105. https://doi.org/10.1590/0001-3765201920190105

Calixto, J. B., Beirith, A., Ferreira, J., Santos, A. R. S., Filho, V. C., & Yunes, R. A. (2000). Naturally occurring antinociceptive substances from plants. *Phytotherapy Research*, *14*(6), 401–418. https://doi.org/10.1002/1099-1573(200009)14:6<>3.0.CO;2-H

Calixto, J. B., Nicolau, M., Pizzolatti, M. G., & Yunes, R. A. (1987). Kinin antagonist activity of compounds from *Mandevilla velutina* in the rat isolated uterus. *British Journal of Pharmacology*, *91*(1), 199–204. https://doi.org/10.1111/j.1476-5381.1987.tb08999.x

Calixto, J. B., Nicolau, M., & Yunes, R. A. (1985). The selective antagonism of bradykinin action on rat isolated uterus by crude *Mandevilla velutina* extract. *British Journal of Pharmacology*, *85*(4), 729–731. https://doi.org/10.1111/j.1476-5381.1985.tb11069.x

Calixto, J. B., Santos, A. R. S., Filho, V. C., & Yunes, R. A. (1998). A review of the plants of the genus *Phyllanthus*: Their chemistry, pharmacology, and therapeutic potential. *Medicinal Research Reviews*, *18*(4), 225–258. https://doi.org/10.1002/(SICI)1098-1128(199807)18:4<>3.0.CO;2-X

Calixto, J. B., & Yunes, R. A. (1986). Effect of a crude extract of *Mandevilla velutina* on contractions induced by bradykinin and [des-Arg^9]-bradykinin in isolated vessels of the rabbit. *British Journal of Pharmacology*, *88*(4), 937–941. https://doi.org/10.1111/j.1476-5381.1986.tb16269.x

Calixto, J. B., & Yunes, R. A. (1991a). Antagonism of kinin-induced contraction of isolated rat uterus by the crude hydroalcoholic extract from *Mandevilla illustris*. *General Pharmacology: The Vascular System*, *22*(1), 99–101. https://doi.org/10.1016/0306-3623(91)90316-X

Calixto, J. B., & Yunes, R. A. (1991b). Natural bradykinin antagonists. *Memórias Do Instituto Oswaldo Cruz*, *86*(suppl 2), 195–202. https://doi.org/10.1590/S0074-02761991000600045

Calixto, J. B., Yunes, R. A., Cruz, A. B., & Medeiros, Y. S. (1992). Effect of compounds from *Mandevilla velutina* on bradykinin-mediated contractile and relaxant responses of the isolated guinea pig trachea. *Agents and Actions*, *36*(3–4), 222–229.

Calixto, J. B., Yunes, R. A., Neto, A. S., Valle, R. M., & Rae, G. A. (1984). Antispasmodic effects of an alkaloid extracted from *Phyllanthus sellowianus*: A comparative study with papaverine. *Brazilian Journal of Medical and Biological Research= Revista Brasileira de Pesquisas Medicas e Biologicas*, *17*(3–4), 313–321.

Calixto, J. (2026). Translating ethnobotany into medicine: Experience from the Brazilian Center for Innovation and Preclinical Studies (CIEnP). *Pharmacological Research – Natural Products*, *11*, 100711. https://doi.org/10.1016/j.prenap.2026.100711

Campos, M. M., Fernandes, E. S., Ferreira, J., Santos, A. R. S., & Calixto, J. B. (2005). Antidepressant-like effects of *Trichilia catigua* (Catuaba) extract: Evidence for dopaminergic-mediated mechanisms. *Psychopharmacology*, *182*(1), 45–53. https://doi.org/10.1007/s00213-005-0052-1

Carvalho, J. T., Teixeira, J. M., Souza, P. J., Bastos, J. K., dos Santos Filho, D., & Sarti, S. J. (1996). Preliminary studies of analgesic and anti-inflammatory properties of *Caesalpinia ferrea* crude extract. *Journal of Ethnopharmacology*, *53*(3), 175–178. https://doi.org/10.1016/0378-8741(96)01441-9

Chaves, J. S., Leal, P. C., Pianowisky, L., & Calixto, J. B. (2008). Pharmacokinetics and tissue distribution of the sesquiterpene α-humulene in mice. *Planta Medica*, *74*(14), 1678–1683.

da Silva, K. A. S., Paszcuk, A. F., Passos, G. F., Silva, E. S., Bento, A. F., Meotti, F. C., & Calixto, J. B. (2011). Activation of cannabinoid receptors by the pentacyclic triterpene α, β-amyrin inhibits inflammatory and neuropathic persistent pain in mice. *Pain*, *152*(8), 1872–1887. https://doi.org/10.1016/j.pain.2011.04.005

De Carvalho, P. M., Rodrigues, R. F. O., Sawaya, A. C. H. F., Marques, M. O. M., & Shimizu, M. T. (2004). Chemical composition and antimicrobial activity of the essential oil of *Cordia verbenacea* D.C. *Journal of Ethnopharmacology*, *95*(2–3), 297–301. https://doi.org/10.1016/j.jep.2004.07.028

De Oliveira, D. D., Da Silva, C. P., Iglesias, B. B., & Beleboni, R. O. (2020). Vitexin possesses anticonvulsant and anxiolytic-like effects in murine animal models. *Frontiers in Pharmacology*, *11*, 1181. https://doi.org/10.3389/fphar.2020.01181

De Souza, L. S., Puziol, L. C., Tosta, C. L., Bittencourt, M. L. F., Ardisson, J. S., Kitagawa, R. R., Filgueiras, P. R., & Kuster, R. M. (2019). Analytical methods to access the chemical composition of an *Euphorbia tirucalli* anticancer latex from traditional Brazilian medicine. *Journal of Ethnopharmacology*, *237*, 255–265. https://doi.org/10.1016/j.jep.2019.03.041

Devereaux, A. L., Mercer, S. L., & Cunningham, C. W. (2018). DARK classics in chemical neuroscience: Morphine. *ACS Chemical Neuroscience*, *9*(10), 2395–2407. https://doi.org/10.1021/acschemneuro.8b00150

Dutra, R. C., Bicca, M. A., Segat, G. C., Silva, K., Motta, E. M., Pianowski, L. F., Costa, R., & Calixto, J. B. (2015). The antinociceptive effects of the tetracyclic triterpene euphol in inflammatory and neuropathic pain models: The potential role of PKCε. *Neuroscience*, *303*, 126–137. https://doi.org/10.1016/j.neuroscience.2015.06.051

Dutra, R. C., Campos, M. M., Santos, A. R. S., & Calixto, J. B. (2016). Medicinal plants in Brazil: Pharmacological studies, drug discovery, challenges and perspectives. *Pharmacological Research*, *112*, 4–29. https://doi.org/10.1016/j.phrs.2016.01.021

Dutra, R. C., Claudino, R. F., Bento, A. F., Marcon, R., Schmidt, E. C., Bouzon, Z. L., Pianowski, L. F., & Calixto, J. B. (2011). Preventive and therapeutic euphol treatment attenuates experimental colitis in mice. *PLoS ONE*, *6*(11), e27122. https://doi.org/10.1371/journal.pone.0027122

Dutra, R. C., da Silva, K. A. B. S., Bento, A. F., Marcon, R., Paszcuk, A. F., Meotti, F. C., Pianowski, L. F., & Calixto, J. B. (2012). Euphol, a tetracyclic triterpene produces antinociceptive effects in inflammatory and neuropathic pain: The involvement of cannabinoid system. *Neuropharmacology*, *63*(4), 593–605. https://doi.org/10.1016/j.neuropharm.2012.05.008

Elsas, S.-M., Rossi, D. J., Raber, J., White, G., Seeley, C.-A., Gregory, W. L., Mohr, C., Pfankuch, T., & Soumyanath, A. (2010). *Passiflora incarnata* L. (passionflower) extracts elicit GABA currents in hippocampal neurons *in vitro*, and show anxiogenic and anticonvulsant effects *in vivo*, varying with extraction method. *Phytomedicine*, *17*(12), 940–949. https://doi.org/10.1016/j.phymed.2010.03.002

European Medicines Agency. 2014. Community herbal monograph on *Passiflora incarnata* L., herba. European Medicines Agency. https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-passiflora-incarnata-l-herba_en.pdf

Falcão, T. R., Araújo, A. A. D., Soares, L. A. L., Farias, I. B. D., Silva, W. A. V. D., Ferreira, M. R. A., Araújo, R. F. D. Jr., Medeiros, J. S. D., Lopes, M. L. D. D. S., & Guerra, G. C. B. (2019). *Libidibia ferrea* fruit crude extract and fractions show anti-inflammatory, antioxidant, and antinociceptive effect *in vivo* and increase cell viability *in vitro*. *Evidence-Based Complementary and Alternative Medicine*, *2019*, 1–14. https://doi.org/10.1155/2019/6064805

Fernandes, E. S., Passos, G. F., Medeiros, R., da Cunha, F. M., Ferreira, J., Campos, M. M., Pianowski, L. F., & Calixto, J. B. (2007). Anti-inflammatory effects of compounds alpha-humulene and (−)-*trans*-caryophyllene isolated from the essential oil of *Cordia verbenacea*. *European Journal of Pharmacology*, *569*(3), 228–236. https://doi.org/10.1016/j.ejphar.2007.04.059

Ferreira, S. H. (1965). A bradykinin-potentiating factor (BPF) present in the venom of *Bothrops jararaca*. *British Journal of Pharmacology and Chemotherapy*, *24*(1), 163. https://doi.org/10.1111/j.1476-5381.1965.tb02091.x

Ferreira, S. H., Greene, L. J., Alabaster, V. A., Bakhle, Y. S., & Vane, J. R. (1970). Activity of various fractions of bradykinin potentiating factor against angiotensin I converting enzyme. *Nature*, *225*(5230), 379–380. https://doi.org/10.1038/225379a0

Fine, P. A., Daly, D. C., & Cameron, K. M. (2005). The contribution of edaphic heterogeneiyt to the evolution and diversity of burseracear trees in the western Amazon. *Evolution*, *59*(7), 1464–1478.

Gambero, A., & Ribeiro, M. (2015). The positive effects of yerba maté (*Ilex paraguariensis*) in obesity. *Nutrients*, *7*(2), 730–750. https://doi.org/10.3390/nu7020730

Godinho, J., De Sa-Nakanishi, A. B., Moreira, L. S., De Oliveira, R. M. W., Huzita, C. H., Mello, J. C. P., Da Silva, A. O. F., Nakamura, C. V., Previdelli, I. S., Ribeiro, M. H. D. M., & Milani, H. (2018). Ethyl-acetate fraction of *Trichilia catigua* protects against oxidative stress and neuroinflammation after cerebral ischemia/reperfusion. *Journal of Ethnopharmacology*, *221*, 109–118. https://doi.org/10.1016/j.jep.2018.04.018

Grundmann, O., Wang, J., McGregor, G., & Butterweck, V. (2008). Anxiolytic activity of a phytochemically characterized *Passiflora incarnata* extract is mediated via the GABAergic system. *Planta Medica*, *74*(15), 1769–1773. https://doi.org/10.1055/s-0028-1088322

Guseinov, M. D., Bobkova, N. V., Svistunov, A. A., Tarasov, V. V., Bokov, D. O., Sergunova, E. V., & Kovaleva, T. (2019). Flavonoids in *Passiflora incarnata* L. dry extract of Russian origin. *Pharmacognosy Journal*, *11*(5), 1143–1147. https://doi.org/10.5530/pj.2019.11.178

IQVIA. (2025). IQVIA report. https://www.iqvia.com/

José, M. F. B., Machado, R. P., Araujo, P. A. B., & Speretta, G. F. (2023). Physiological effects of yerba maté (*Ilex paraguariensis*): A systematic review. *Nutrition Reviews*, *81*(9), 1163–1179. https://doi.org/10.1093/nutrit/nuac109

Kassuya, C. A., Silvestre, A. A., Rehder, V. L. G., & Calixto, J. B. (2003). Anti-allodynic and anti-oedematogenic properties of the extract and lignans from *Phyllanthus amarus* in models of persistent inflammatory and neuropathic pain. *European Journal of Pharmacology*, *478*(2–3), 145–153. https://doi.org/10.1016/j.ejphar.2003.08.079

Law No. 13,123 of May 20, 2015. (2015). http://www.planalto.gov.br/ccivil_03/_ato2015-2018/2015/lei/l13123.htm

Leal, L. K. A. M., Silva, A. H., & Viana, G. S. D. B. (2017). *Justicia pectoralis*, a coumarin medicinal plant have potential for the development of anti-asthmatic drugs? *Revista Brasileira de Farmacognosia*, *27*(6), 794–802. https://doi.org/10.1016/j.bjp.2017.09.005

Lima, N. D. S., Franco, J. G., Peixoto-Silva, N., Maia, L. A., Kaezer, A., Felzenszwalb, I., De Oliveira, E., De Moura, E. G., & Lisboa, P. C. (2014). *Ilex paraguariensis* (yerba mate) improves endocrine and metabolic disorders in obese rats primed by early weaning. *European Journal of Nutrition*, *53*(1), 73–82. https://doi.org/10.1007/s00394-013-0500-3

Macêdo, N. S., Silveira, Z. D. S., Bezerra, A. H., Costa, J. G. M. D., Coutinho, H. D. M., Romano, B., Capasso, R., Cunha, F. A. B. D., & Da Silva, M. V. (2020). *Caesalpinia ferrea* C. Mart. (Fabaceae) phytochemistry, ethnobotany, and bioactivities: A review. *Molecules*, *25*(17), 3831. https://doi.org/10.3390/molecules25173831

Martim, J. K. P., Maranho, L. T., & Costa-Casagrande, T. A. (2021). Review: Role of the chemical compounds present in the essential oil and in the extract of *Cordia verbenacea* DC as an anti-inflammatory, antimicrobial and healing product. *Journal of Ethnopharmacology*, *265*, 113300. https://doi.org/10.1016/j.jep.2020.113300

Matos, I., Bento, A. F., Marcon, R., Claudino, R. F., & Calixto, J. B. (2013). Preventive and therapeutic oral administration of the pentacyclic triterpene α, β-amyrin ameliorates dextran sulfate sodium-induced colitis in mice: The relevance of cannabinoid system. *Molecular Immunology*, *54*(3–4), 482–492. https://doi.org/10.1016/j.molimm.2013.01.018

Mattos, W. M., Campos, M. M., Fernandes, E. S., Richetti, G. P., Niero, R., Yunes, R. A., & Calixto, J. B. (2006). Anti-edematogenic effects of velutinol A isolated from *Mandevilla velutina*: Evidence for a selective inhibition of kinin B1 receptor-mediated responses. *Regulatory Peptides*, *136*(1–3), 98–104. https://doi.org/10.1016/j.regpep.2006.04.011

Mattos, W. M., Ferreira, J., Richetti, G. P., Niero, R., Yunes, R. A., & Calixto, J. B. (2006). Antinociceptive properties produced by the pregnane compound velutinol A isolated from *Mandevilla velutina*. *Neuropeptides*, *40*(2), 125–132. https://doi.org/10.1016/j.npep.2005.12.001

McGregor, G., Grundmann, O., Wang, J., & Butterweck, V. (2008). Antianxiety effects of a passion flower extract (*Passiflora incarnata* L.) in animal models of anxiety. *Zeitschrift für Phytotherapie*, *29*(S 1), s-2008-1047867. https://doi.org/10.1055/s-2008-1047867

Medeiros, R., Otuki, M. F., Avellar, M. C. W., & Calixto, J. B. (2007). Mechanisms underlying the inhibitory actions of the pentacyclic triterpene α-amyrin in the mouse skin inflammation induced by phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate. *European Journal of Pharmacology*, *559*(2–3), 227–235. https://doi.org/10.1016/j.ejphar.2006.12.005

Mendes, F. R., & Carlini, E. A. (2007). Brazilian plants as possible adaptogens: An ethnopharmacological survey of books edited in Brazil. *Journal of Ethnopharmacology*, *109*(3), 493–500. https://doi.org/10.1016/j.jep.2006.08.024

Montinari, M. R., Minelli, S., & De Caterina, R. (2019). The first 3500 years of aspirin history from its roots—A concise summary. *Vascular Pharmacology*, *113*, 1–8. https://doi.org/10.1016/j.vph.2018.10.008

Moura, C. T. M., Batista-Lima, F. J., Brito, T. S., Silva, A. A. V., Ferreira, L. C., Roque, C. R., Aragão, K. S., Havt, A., Fonseca, F. N., Leal, L. K. A. M., & Magalhães, P. J. C. (2017). Inhibitory effects of a standardized extract of *Justicia pectoralis* in an experimental rat model of airway hyper-responsiveness. *Journal of Pharmacy and Pharmacology*, *69*(6), 722–732. https://doi.org/10.1111/jphp.12689

Neves, P. C., Neves, M. C., Cruz, A. B., Sant'Ana, A. E., & Yunes, R. A. (1993). Differential effects of *Mandevilla velutina* compounds on paw oedema induced by phospholipase A_2 and phospholipase C. *European Journal of Pharmacology*, *243*(3), 213–219.

Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products*, *83*(3), 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

Ngamkitidechakul, C., Jaijoy, K., Hansakul, P., Soonthornchareonnon, N., & Sireeratawong, S. (2010). Antitumour effects of *Phyllanthus emblica* L.: Induction of cancer cell apoptosis and inhibition of *in vivo* tumour promotion and *in vitro* invasion of human cancer cells. *Phytotherapy Research*, *24*(9), 1405–1413. https://doi.org/10.1002/ptr.3127

Nunes, T. R. D. S., Cordeiro, M. F., Beserra, F. G., Souza, M. L. D., Silva, W. A. V. D., Ferreira, M. R. A., Soares, L. A. L., Costa-Junior, S. D., Cavalcanti, I. M. F., Pitta, M. G. D. R., Pitta, I. D. R., & Rêgo, M. J. B. D. M. (2018). Organic extract of *Justicia pectoralis* Jacq. leaf inhibits interferon-γ secretion and has bacteriostatic activity against *Acinetobacter baumannii* and *Klebsiella pneumoniae*. *Evidence-Based Complementary and Alternative Medicine*, *2018*(1), 5762368. https://doi.org/10.1155/2018/5762368

Oliveira, C. H., Moraes, M. E. A., Moraes, M. O., Bezerra, F. A., Abib, E., & Nucci, G. D. (2005). Clinical toxicology study of an herbal medicinal extract of *Paullinia cupana*, *Trichilia catigua*, *Ptychopetalum olacoides* and *Zingiber officinale* (Catuama®) in healthy volunteers. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *19*(1), 54–57. https://doi.org/10.1002/ptr.1484

Oliveira, F. A., Costa, C. L., Chaves, M. H., Almeida, F. R., Cavalcante, Í. J., Lima, A. F., Lima, R. C. Jr., Silva, R. M., Campos, A. R., & Santos, F. A. (2005). Attenuation of capsaicin-induced acute and visceral nociceptive pain by α-and β-amyrin, a triterpene mixture isolated from *Protium heptaphyllum* resin in mice. *Life Sciences*, *77*(23), 2942–2952. https://doi.org/10.1016/j.lfs.2005.05.031

Oliveira, L. M. N. D., Bastos, M. D. S. R., Lima, A. C. S. D., Figueiredo, E. A. T. D., Dias, F. G. B., Silva, L. M. R. D., Benevides, S. D., Ribeiro, P. R. V., Sabino, L. B. D. S., & Figueiredo, R. W. D. (2023). Chemical characterization, cytotoxicity, antimicrobial and antioxidant potential of *Justicia pectoralis* Jacq and Croton jacobinensis Baill extracts. *Brazilian Journal of Pharmaceutical Sciences*, *59*, e21224. https://doi.org/10.1590/s2175-97902023e21224

Ondetti, M. A., Rubin, B., & Cushman, D. W. (1977). Design of specific inhibitors of angiotensin-converting enzyme: New class of orally active antihypertensive agents. *Science*, *196*(4288), 441–444. https://doi.org/10.1126/science.191908

Passos, G. F., Fernandes, E. S., Da Cunha, F. M., Ferreira, J., Pianowski, L. F., Campos, M. M., & Calixto, J. B. (2007). Anti-inflammatory and anti-allergic properties of the essential oil and active compounds from *Cordia verbenacea*. *Journal of Ethnopharmacology*, *110*(2), 323–333. https://doi.org/10.1016/j.jep.2006.09.032

Passos, G. F., Medeiros, R., Marcon, R., Nascimento, A. F., Calixto, J. B., & Pianowski, L. F. (2013). The role of PKC/ERK1/2 signaling in the anti-inflammatory effect of tetracyclic triterpene euphol on TPA-induced skin inflammation in mice. *European Journal of Pharmacology*, *698*(1–3), 413–420. https://doi.org/10.1016/j.ejphar.2012.10.019

Pereira, D. F., Kappel, V. D., Cazarolli, L. H., Boligon, A. A., Athayde, M. L., Guesser, S. M., Da Silva, E. L., & Silva, F. R. M. B. (2012). Influence of the traditional Brazilian drink *Ilex paraguariensis* tea on glucose homeostasis. *Phytomedicine*, *19*(10), 868–877. https://doi.org/10.1016/j.phymed.2012.05.008

Pimentel, G. D., Lira, F. S., Rosa, J. C., Caris, A. V., Pinheiro, F., Ribeiro, E. B., do Nascimento, C. M. O., & Oyama, L. M. (2013). Yerba mate extract (*Ilex paraguariensis*) attenuates both central and peripheral inflammatory effects of diet-induced obesity in rats. *The Journal of Nutritional Biochemistry*, *24*(5), 809–818. https://doi.org/10.1016/j.jnutbio.2012.04.016

Pizzolatti, M. G., Venson, A. F., Júnior, A. S., Smânia, E. D. F., & Braz-Filho, R. (2002). Two epimeric flavalignans from *Trichilia catigua* (Meliaceae) with antimicrobial activity. *Zeitschrift Für Naturforschung C*, *57*(5–6), 483–488. https://doi.org/10.1515/znc-2002-5-614

Pizzolatti, M. G., Verdi, L. G., Brighente, I. M. C., Dos Santos Madureira, L. A., & Braz Filho, R. (2004). Minor γ-lactones from *Trichilia catigua* (Meliaceae) and its precursors by GC-MS. *Natural Product Research*, *18*(5), 433–438. https://doi.org/10.1080/14786410310001630582

REFLORA. (2026). Flora e funga do Brasil. https://floradobrasil.jbrj.gov.br/consulta/#CondicaoTaxonCP

Rocha e Silva, M., Beraldo, W. T., & Rosenfeld, G. (1949). Bradykinin, a hypotensive and smooth muscle stimulating factor released from plasma globulin by snake venoms and by trypsin. *American Journal of Physiology-Legacy Content*, *156*(2), 261–273. https://doi.org/10.1152/ajplegacy.1949.156.2.261

Rogerio, A. P., Andrade, E. L., Leite, D. F. P., Figueiredo, C. P., & Calixto, J. B. (2009). Preventive and therapeutic anti-inflammatory properties of the sesquiterpene α-humulene in experimental airways allergic inflammation. *British Journal of Pharmacology*, *158*(4), 1074–1087. https://doi.org/10.1111/j.1476-5381.2009.00177.x

Rosa Júnior, I. A., Almeida, D. D. S., Napolitano, H. B., Peixoto, J. D. C., Rosseto, L. P., Hungria Pinto, E. M., Dias, L. D., Fajemiroye, J. O., Costa, E. A., Vieira, R. P., & Martins, J. L. R. (2024). Evaluation of gastroprotective activity of the methanolic extract of *Justicia pectoralis* Jacq. (Acanthaceae). *Nutrients*, *16*(10), 1430. https://doi.org/10.3390/nu16101430

Segat, G. C., Manjavachi, M. N., Matias, D. O., Passos, G. F., Freitas, C. S., Costa, R., & Calixto, J. B. (2017). Antiallodynic effect of β-caryophyllene on paclitaxel-induced peripheral neuropathy in mice. *Neuropharmacology*, *125*, 207–219. https://doi.org/10.1016/j.neuropharm.2017.07.015

Sertié, J. A. A., Basile, A. C., Panizza, S., Oshiro, T. T., Azzolini, C. P., & Penna, S. C. (1991). Pharmacological assay of *Cordia verbenacea* III: Oral and topical antiinflammatory activity and gastrotoxicity of a crude leaf extract. *Journal of Ethnopharmacology*, *31* (2), 239–247. https://doi.org/10.1016/0378-8741(91)90008-2

Sertié, J. A. A., Basile, A., Panizza, S., Matida, A., & Zelnik, R. (1988). Pharmacological assay of *Cordia verbenacea*; part 1. Anti-inflammatory activity and toxicity of the crude extract of the leaves. *Planta Medica*, *54*(1), 7–10. https://doi.org/10.1055/s-2006-962318

Sertié, J. A. A., Woisky, R. G., Wiezel, G., & Rodrigues, M. (2005). Pharmacological assay of *Cordia verbenacea* V: Oral and topical anti-inflammatory activity, analgesic effect and fetus toxicity of a crude leaf extract. *Phytomedicine*, *12*(5), 338–344. https://doi.org/10.1016/j.phymed.2003.09.013

Siani, A. C., Ramos, M. D. S., Menezes-de-Lima, O. Jr., Ribeiro-dos-Santos, R., Fernadez-Ferreira, E., Soares, R. O. A., Rosas, E. C., Susunaga, G. S., Guimarães, A. C., Zoghbi, M. D. G., & Henriques, M. D. G. (1999). Evaluation of anti-inflammatory-related activity of essential oils from the leaves and resin of species of *Protium*. *Journal of Ethnopharmacology*, *66*(1), 57–69. https://doi.org/10.1016/s0378-8741(98)00148-2

Silva, A. C. P., de Faria, D. E. P., Santo Borges, N. B. D. E., de Souza, I. A., Peters, V. M., & de Oliveira Guerra, M. (2007). Toxicological screening of *Euphorbia tirucalli* L.: Developmental toxicity studies in rats. *Journal of Ethnopharmacology*, *110*(1), 154–159. https://doi.org/10.1016/j.jep.2006.09.012

Silva, R. M. G. D., Barbosa, F. C., Santos, H. H., Granero, F. O., Figueiredo, C. C. M., Nicolau-Junior, N., Hamaguchi, A., & Silva, L. P. (2025). Antioxidant and anti-glycation activities of *Mandevilla velutina* extract and effect on parasitemia levels in *Trypanosoma cruzi* experimental infection: *In vivo*, *in vitro* and *in silico* approaches. *Journal of Ethnopharmacology*, *337*, 118994. https://doi.org/10.1016/j.jep.2024.118994

Swissmedic. (2006). *Pharmacopoea Helvetica* (10th ed.). Swissmedic.

Timalsina, D., Pokhrel, K. P., & Bhusal, D. (2021). Pharmacologic activities of plant-derived natural products on respiratory diseases and inflammations. *BioMed Research International*, *2021*(1), 1636816. https://doi.org/10.1155/2021/1636816

Tolouei, S. E. L., Macedo Júnior, S. J., Potrich, F. B., De Andrade, E. L., Dos Santos, A. Á., Freitas, C. S., Heller, M., Vilela, F. C., Rocha, R. F., Zimath, P., Fadanni, G. P., Marques, N. F., De Mesquita, F. C., Pereira, A. M. S., Correia, D., Marcon, R., Siqueira Júnior, J. M., & Calixto, J. B. (2026). Preclinical safety and anti-inflammatory activity of

a standardized *Justicia pectoralis* Jacq. extract in experimental models of respiratory inflammation. *Journal of Ethnopharmacology*, *363*, 121411. https://doi.org/10.1016/j.jep.2026.121411

Tolouei, S. E. L., Marcon, R., Vilela, F. C., Freitas, C. S., Heller, M., de Andrade, E. L., Macedo Júnior, S. J., Santos, A. Á. D., Rocha, R. F., Fadanni, G. P., Marques, N. F., Siqueira Júnior, J. M., & Calixto, J. B. (2025). Preclinical development of a standardized extract of *Ilex paraguariensis* A.St.-Hil for the treatment of obesity and metabolic syndrome. *Pharmacological Research*, *213*, 107607. https://doi.org/10.1016/j.phrs.2025.107607

Valenca, H. D. M., e Silva, C. P., de Brito Gitirana, L., Valença, S. S., & Lanzetti, M. (2022). Beneficial effects of *Ilex paraguariensis* in the prevention of obesity-associated metabolic disorders in mice. *Phytotherapy Research*, *36*(2), 1032–1042. https://doi.org/10.1002/ptr.7377

Viana, A. F., Maciel, I. S., Motta, E. M., Leal, P. C., Pianowski, L., Campos, M. M., & Calixto, J. B. (2011). Antinociceptive activity of *Trichilia catigua* hydroalcoholic extract: New evidence on its dopaminergic effects. *Evidence-Based Complementary and Alternative Medicine*, *2011*(1), 120820. https://doi.org/10.1093/ecam/nep144

Vitor, C. E., Figueiredo, C. P., Hara, D. B., Bento, A. F., Mazzuco, T. L., & Calixto, J. B. (2009). Therapeutic action and underlying mechanisms of a combination of two pentacyclic triterpenes, α-and β-amyrin, in a mouse model of colitis. *British Journal of Pharmacology*, *157*(6), 1034–1044. https://doi.org/10.1111/j.1476-5381.2009.00271.x

Wieczfinska, J., Sitarek, P., Kowalczyk, T., Skała, E., & Pawliczak, R. (2020). The anti-inflammatory potential of selected plant-derived compounds in respiratory diseases. *Current Pharmaceutical Design*, *26*(24), 2876–2884. https://doi.org/10.2174/1381612826666200406093257

How to cite this article: Hoepers, J. V. A., Takasumi, L. C. N., & Calixto, J. B. (2026). Translating Brazilian medicinal plants into therapeutic innovation: Preclinical evidence and lessons learned. *British Journal of Pharmacology*, 1–21. https://doi.org/10.1111/bph.70589