UNLOCKING NEW PHARMACOLOGICAL PERSPECTIVES ON *Piper umbellatum* L.: A 2014–2024 MINI-REVIEW

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ABSTRACT: *Piper umbellatum* L. (Piperaceae), commonly known as "pimenteira" or "caapeba" in Brazil, has traditionally been used to treat wounds, ulcers, fever, pain, and disorders of the digestive, hepatic, and lymphatic systems. This review aimed to address the following question: What are the recent advances and gaps in the pharmacological knowledge of *P. umbellatum* from 2014 to 2024? To this end, 24 studies published in Portuguese or English were selected and analyzed from databases such as SciFinder®, Scopus, PubMed, and ScienceDirect. Brazil was the primary study location, followed by Cameroon. The leaves and polar extracts were the most frequently investigated plant parts. Novel *in vitro* activities were identified, including antischistosomal, filaricidal, insecticidal, and herbicidal effects. *In vivo* studies revealed protective effects against colitis and gastric damage, as well as reproductive benefits. The convergence between traditional uses and scientific evidence highlights the therapeutic potential of this species for various conditions, including its use as an aphrodisiac.
KEYWORDS: *Piper umbellatum* L.; Literature Review; *In vitro*; *In vivo*, Biological Assay; Brazil.

DESVENDANDO NOVAS PERSPECTIVAS FARMACOLÓGICAS SOBRE *Piper umbellatum* L.: UMA MINIRREVISÃO (2014–2024)

RESUMO: *Piper umbellatum* L. (Piperaceae), comumente conhecida como "pimenteira" ou "caapeba" no Brasil, tem sido tradicionalmente utilizada no tratamento de feridas, úlceras, febre, dores e distúrbios dos sistemas digestivo, hepático e linfático. Esta revisão teve como objetivo responder à seguinte pergunta: quais são os avanços recentes e as lacunas no conhecimento farmacológico sobre *P. umbellatum* no período de 2014 a 2024? Para isso, foram selecionados e analisados 24 estudos publicados em português ou inglês, obtidos em bases de dados como SciFinder®, Scopus, PubMed e ScienceDirect. O Brasil foi o principal local de realização dos estudos, seguido por Camarões. As folhas e os extratos polares foram as partes da planta mais investigadas. Foram identificadas novas atividades *in vitro*, incluindo efeitos antiesquistossomóticos, filaricidas, inseticidas e herbicidas. Estudos *in vivo* revelaram efeitos protetores contra colite e lesões gástricas, bem como benefícios reprodutivos. A convergência entre os usos tradicionais e as evidências científicas destaca o potencial terapêutico dessa espécie para diversas condições, incluindo seu uso como afrodisíaco.

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PALAVRAS-CHAVE: *Piper umbellatum* L.; Revisão de Literatura; *In vitro*; *In vivo*; Ensaio Biológico; Brasil.

REVELANDO NUEVAS PERSPECTIVAS FARMACOLÓGICAS SOBRE *Piper umbellatum* L.: UNA MINIRREVISIÓN (2014–2024)

RESUMEN: *Piper umbellatum* L. (Piperaceae), conocida comúnmente como “pimenteira” o “caapeba” en Brasil, ha sido utilizada tradicionalmente para tratar heridas, úlceras, fiebre, dolor y trastornos de los sistemas digestivo, hepático y linfático. Esta revisión tuvo como objetivo abordar la siguiente pregunta: ¿cuáles son los avances recientes y las brechas en el conocimiento farmacológico sobre *P. umbellatum* entre 2014 y 2024? Para ello, se seleccionaron y analizaron 24 estudios publicados en portugués o inglés, a partir de bases de datos como SciFinder®, Scopus, PubMed y ScienceDirect. Brasil fue el principal país de realización de los estudios, seguido de Camerún. Las hojas y los extractos polares fueron las partes más investigadas de la planta. Se identificaron nuevas actividades *in vitro*, incluyendo efectos antiesquistosómicos, filaricidas, insecticidas y herbicidas. Los estudios *in vivo* revelaron efectos protectores contra la colitis y el daño gástrico, así como beneficios reproductivos. La convergencia entre los usos tradicionales y la evidencia científica resalta el potencial terapéutico de esta especie para diversas afecciones, incluido su uso como afrodisíaco.
PALABRAS CLAVE: *Piper umbellatum* L.; Revisión de la Literatura; *In vitro*; *In vivo*; Ensayo Biológico; Brasil.

1. INTRODUCTION

Piper umbellatum L. (Piperaceae) is found throughout South America, including Brazil, Bolivia, Colombia, Guyana, Peru, Paraguay, and Venezuela. In Brazil, its geographical distribution spans the North, Central-West, and South regions, with the highest prevalence in the Northeast and Southeast, totaling approximately 1,446 occurrence records. Of these, 382 are human observations added to the Brazilian Biodiversity Information Facility Repository (*Sistema de Informação sobre a Biodiversidade Brasileira*), although *P. umbellatum* is not considered endemic (SiBBr, 2025; Guimarães; Medeiros; Queiroz, 2025). The species is known by several synonyms, including *Pothomorphe umbellata* (L.) Miq., *Peperomia umbellata* (L.) Kunth, *Peperomia sidaefolia* A. Dietr., *Piper dombeyanum* (Miq.) C.DC., *Piper sidaefolium* Link & Otto, *Piper subpeltatum var. sidaefolium* (Link & Otto) C.DC., *Piper subpeltatum* Willd., and *Pothomorphe sidifolia* (Link & Otto) Miq. (Guimarães; Medeiros; Queiroz, 2025). Popular names for the plant include caapeba, aguaxuma, guaxima, capeua, catage, malva disco, malvaísco, matico de Puna, moho, pariparoba, paripoba, periparoba, and pimenta rabuda (Base de Dados Bibliográfica das Plantas Nativas usadas pelos Brasileiros (DATAPLAMT, 2025).

The plant is a subshrub with an erect growth habit, covered with trichomes, and characterized by large ovate leaves measuring approximately 18 to 25 centimeters in length and 20 to 35 centimeters in width. The leaves display a rounded to ovate or reniform shape, with a cordate base resembling a rounded "V" and an abruptly acuminate apex. Its flowers are white or yellowish, arranged in spike-like inflorescences (Guimarães; Medeiros; Queiroz, 2025; Yuncker, 1973).

In Brazilian traditional medicine, all parts of the plant are used—mainly to treat wounds, ulcers, and fever, as well as hemoptysis, jaundice, chronic cough, and pain disorders associated with arthritis, rheumatism, hemorrhoids, and other conditions affecting the nervous system, stomach, liver, spleen, and lymphatic system DATAPLAMT, 2025; Da Matta, 2003; Peckolt, 1941). Tinctures, as well as leaves and stems for tea and massage gels, are available for purchase on Brazilian websites (Aura e Pele, 2025; Americanas, 2025).

Popularly known also as "capeba" in Brazil, the young leaves are commonly eaten raw in salads, whereas the older, blanched leaves are used to prepare stuffed rolls filled with meat and spices (Cavalcante *et al*., 2023; Silva; Costa; Murta, 2021; Corrêa, 1909). Leaves from specimens collected in Malaysia have been reported to be rich in potassium, calcium, magnesium, and vitamin C; however, they also contain high levels of phytates, which may reduce the bioavailability of these nutrients (Saupi *et al*., 2021).

A previous review on *P. umbellatum*, covering literature published up to 2009, documented its use in 24 countries. Despite the wide range of traditional applications, there is a consensus that its primary indications are for kidney-related conditions (including diuretic purposes), stomachaches, and wound treatment, with Brazil having the highest number of recorded uses and scholarly publications on the species (Roersch, 2010). These findings are further supported by several historical records that document the medicinal use of “caapeba” in Brazil found in texts dating back to the 17 th century (DATAPLAMT, 2025; Vasconcelos, 1977).

Despite Brazil’s long-standing tradition in the use of medicinal plants and its efforts to institutionalize phytotherapy through policies such as the National Policy on Medicinal Plants and Phytotherapy (PNPMF – Decree No. 5,813, of June 22, 2006), *P. umbellatum* remains absent from the country’s main official lists, including the National List of Essential Medicines (RENAME) and the National List of Medicinal Plants of Interest to the SUS (RENISUS) (Brasil, 2024, 2009, 2006).This omission is particularly striking given that the species appeared in the first edition of the Brazilian Official Pharmacopoeia, published in 1929, under the name *Heckeria umbellata*, with indications for the use of its dried root in the treatment of liver disorders, jaundice, stomach problems, and as a diuretic and febrifuge (Brandão *et al*., 2009). Brazil began organizing essential medicines lists in 1964, with the publication of Decree No. 53,612 on December 26, 1964, which established the Basic and Priority List of Biological Products and Materials for Human and Veterinary Pharmaceutical Use (Brasil, 1964). In 2009, RENISUS was created, listing 71 plant species with therapeutic potential, with the aim of guiding the production chain and the development of research in the country (Brasil, 2022). Currently, 12 herbal medicines are available to the population through RENAME, in line with World Health Organization recommendations (Brasil, 2024; WHO, 2013), aiming to ensure safe access to and rational use of medicinal plants. Even so, *P. umbellatum* remains without institutional recognition.

However, the academic community continues to investigate this medicinal plant, with new biological properties being reported since 2010. This indicates that there is still significant potential to be explored in its biological and chemical characteristics. This review compiles recent studies on *P. umbellatum*, with an emphasis on findings not addressed in previous reviews, highlighting key advances and the remaining gaps in the research on this species.

2. METHODOLOGY

This study is a literature review that analyzes and compares scientific data published before 2014 about *Piper umbellatum* L. and reported by Roersch (2010).

This review examined original publications in English and Portuguese, based on research conducted between September 2024 and February 2025, using databases such as SciFinder®, Scopus, PubMed and ScienceDirect. The search was performed using only the descriptors "*Piper umbellatum*" OR "*Pothomorphe umbellata*", without combining additional terms or Boolean operators. The results were then refined using the filters offered by each database (publication period 2014-2024, language, and document type).

Articles identified through title analysis across the four databases were imported into Rayyan. After duplicate removal, two independent reviewers screened the records by reading titles and abstracts and applying the predefined eligibility criteria. The inclusion criteria comprised original studies reporting biological activities of *P. umbellatum*.

Exclusion criteria encompassed articles focusing on phytochemical composition, germination or propagation, nutrient or component quantification, ethnopharmacological or traditional uses, as well as review articles, mini-reviews, opinion pieces, theoretical discussions, and methodological papers.

Discrepancies between reviewers were resolved through discussion during full-text screening. In several instances, full-text examination was necessary to confirm whether *P. umbellatum* was indeed included among the species investigated. During full-text assessment, additional studies were excluded for presenting non-relevant biological activities such as antioxidant effects, for reporting only preliminary antimicrobial activity evaluated exclusively by diffusion-agar methods or, inactive results for *P. umbellatum*.

Data from the selected articles were systematically extracted and recorded in a Microsoft Office Excel® spreadsheet. The studies were organized chronologically in descending order and grouped according to *in vitro* and *in vivo* experimental models.

For *in vitro* assays, the following information was extracted: collection site, part of the plant studied, solvent used for extraction or compound tested, concentration tested or IC_{50}/EC_{50}/MIC values, biological model or organism, and observed results. For *in vivo* assays, data were organized based on route of administration, dose (mg/kg), treatment scheme, animal species/gender/number per group, animal model, and biological results.

The biological activities identified were compared to the traditional uses reported by Roersch (2010). The extracted and organized data (Supplementary material) were synthesized narratively, and the findings were presented using descriptive text, and tables.

3. RESULTS AND DISCUSSION

3.1 Relevant chemical investigations

Early phytochemical studies (Figure 1) reported isolation of triterpenes (friedelin, amyrin), sterols (*β*-sitosterol, its *β*-sitosterol glucoside and its 3-O-*β*-D-[6'-dodecanoyl]-glucopyranoside), a variety of flavonoids (wogonin, apigenin 8-C-neohesperidoside, acacetin 6-C-*β*-D-glucopyranoside), chalcone uvangoletin, and phenylpropanoid amides compounds (N-*p*-coumaroyl tyramine, N-*trans*-feruloyltyramine) from *Piper umbellatum* L. Additional compounds identified before 2010 include catechol derivatives, most notably 4-nerolidylcatechol, together with amide-type alkaloids such as piperumbellactams A–D, the aporphine alkaloid N-hydroxyaristolam II, and the phenethylamine-type alkaloid N-benzoylmescaline (Tapopda *et al*., 2008; Isobe *et al*., 2002). After 2010, were isolated (Figure 1) amide alkaloids, cepharadiones A and B, flavone glycosides, isovitexin, and rhoifoline (apigenin 7-*O*-neohesperidoside) and, three disaccharides (Tapopda *et al*., 2012).

Post-2010 studies expanded this chemical profile by quantifying several classes of phytochemicals from fruits and leaves of *P. umbellatum*. In an early quantitative study, thirteen compounds were detected in fruits and leaves, with terpenoids occurring in comparatively higher amounts than piperamides and phenolics, followed by flavonoids as the second major group. Total of flavonoids and terpenoids contents were higher in fruits than in leaves, with ursolic acid and quercetin identified as the major constituents in the fruits (Chandra *et al*., 2015). More recently, a broader phytochemical profiling of the leaves confirmed the presence of terpenoids, sterols, glycosides, flavonoids, alkaloids, and phenolic acids, as well as classes of natural products not previously reported for the species, including saponins, lignans, stilbenes, and tannins. The study also highlighted particularly high concentrations of phenolic acids, tannins, flavonoids, and stilbenes (Peters, Baradum, Ohiri, 2022).

Notably, several of these metabolites (Figure 1) also exhibit biological activities. The alkaloid N-benzoylmescaline and the flavonoid wogonin inhibit *Helicobacter pylori* at MIC values of 2.5 μg/mL and 12.5 μg/mL, respectively (Isobe *et al*., 2002). In addition, piperumbellactams B and C, as well as N-*p*-coumaroyl tyramine, demonstrate DPPH radical-scavenging activity with IC_{50} values below 20 μM. Piperumbellactam A and N-hydroxyaristolam II also show antifungal effects against *Candida albicans*, *C. glabrata* and *Microsporum canis* at 200 μg/mL, with activities superior to those of 4-nerolidylcatechol (Tapopda *et al*., 2008).

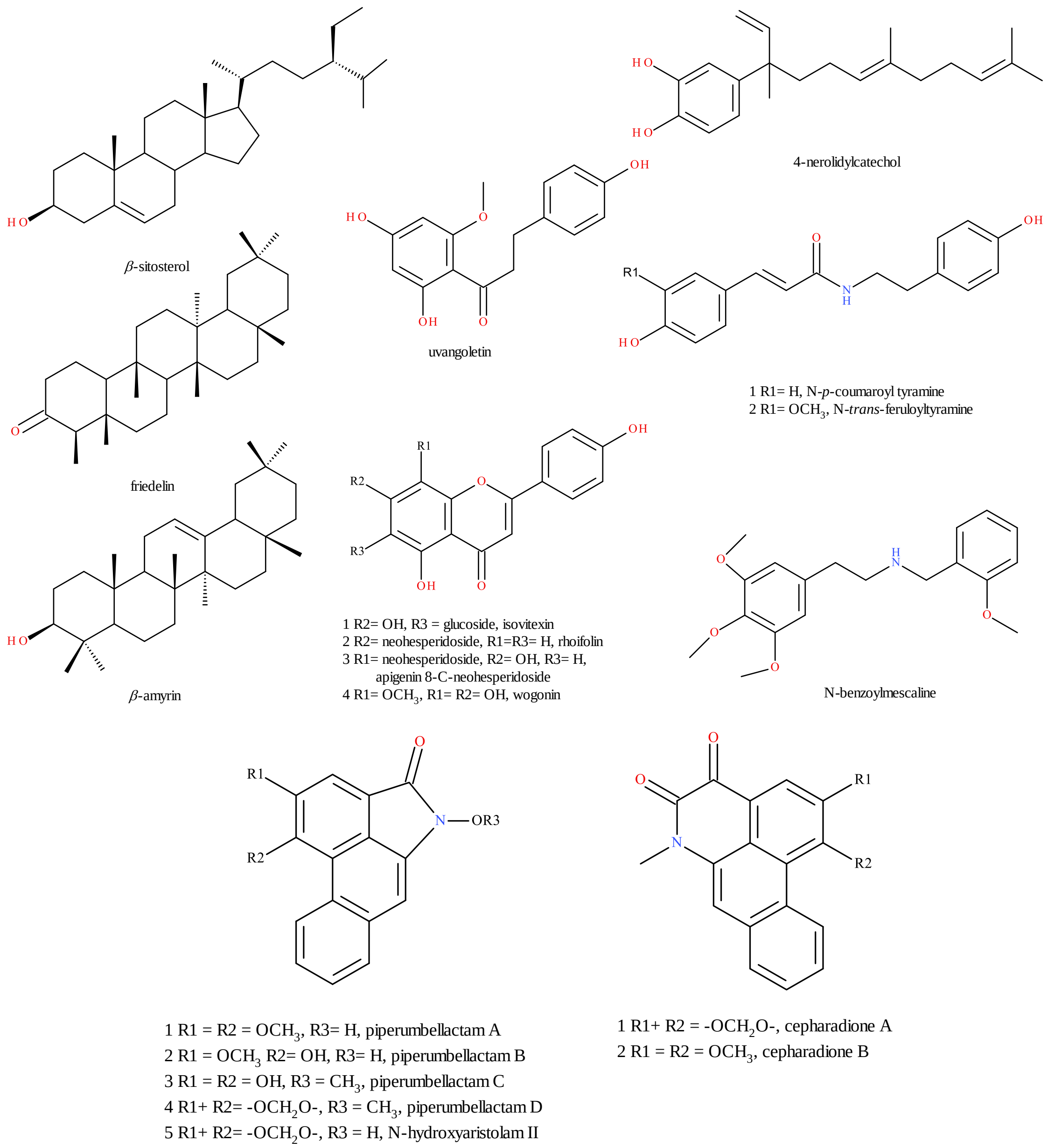


Figure 1: Structures of isolated compounds of *P. umbellatum*.

Complementing the isolated constituents, the composition of *P. umbellatum* essential oils further reinforces the chemical distinctiveness of the species. Essential oils analyzed, predominantly from populations in the southeastern region of Brazil, show a consistent sesquiterpene profile dominated by germacrene D (8.6%-65.5%), bicyclogermacrene (8.95%-11.8%) and (*E*)-caryophyllene (5.39%-21.77%) (Figure 2). In contrast, material collected in Goiás displayed *β*-selinene (16.12%) as its major component, indicating a distinct chemical profile relative to southeastern populations (de Oliveira *et al*., 2024; Krinski, Foerster, Deschamps, 2018; Perigo *et al*., 2016; Mattana *et al*., 2015; Morandim-Giannetti *et al*., 2010; Mesquita *et al*., 2005).

Table 1: Summary of three main compounds found in *Piper umbellatum* L. essential oils.

Collection site (part of plant)	**Compound concentration (%)**	**Reference**
Ilhéus, Bahia (leaves)	Germacrene D (26.33) (*E*)-Caryophyllene (21.77) Bicyclogermacrene (10.24)	Oliveira *et al.*, 2024
Goiás (leaves)	*β*-selinene (16.12) Bicyclogermacrene (10.64) (*E*)-Caryophyllene (5.39)	Krinski, Foerster, Deschamps, 2018
Campinas, São Paulo (leaves)	Germacrene D (55.8) Bicyclogermacrene (11.8) (*E*)-Caryophyllene (6.3)	Perigo *et al.*, 2016
Cajamar, São Paulo (leaves)	Germacrene D (65.5) *α*-Selinene (9.7) (*E*)-Caryophyllene (7.5)	Mattana *et al.*, 2015
Araraquara, São Paulo (leaves)	Germacrene D (34.19) γ-Cadinene (15.02) Bicyclogermacrene (8.95)	Morandim-Giannetti *et al.*, 2010
Minas Gerais (leaves)	(*E*)-Caryophyllene (12.6) Bicyclogermacrene (10.1) Germacrene D (8.6)	Mesquita *et al.*, 2005

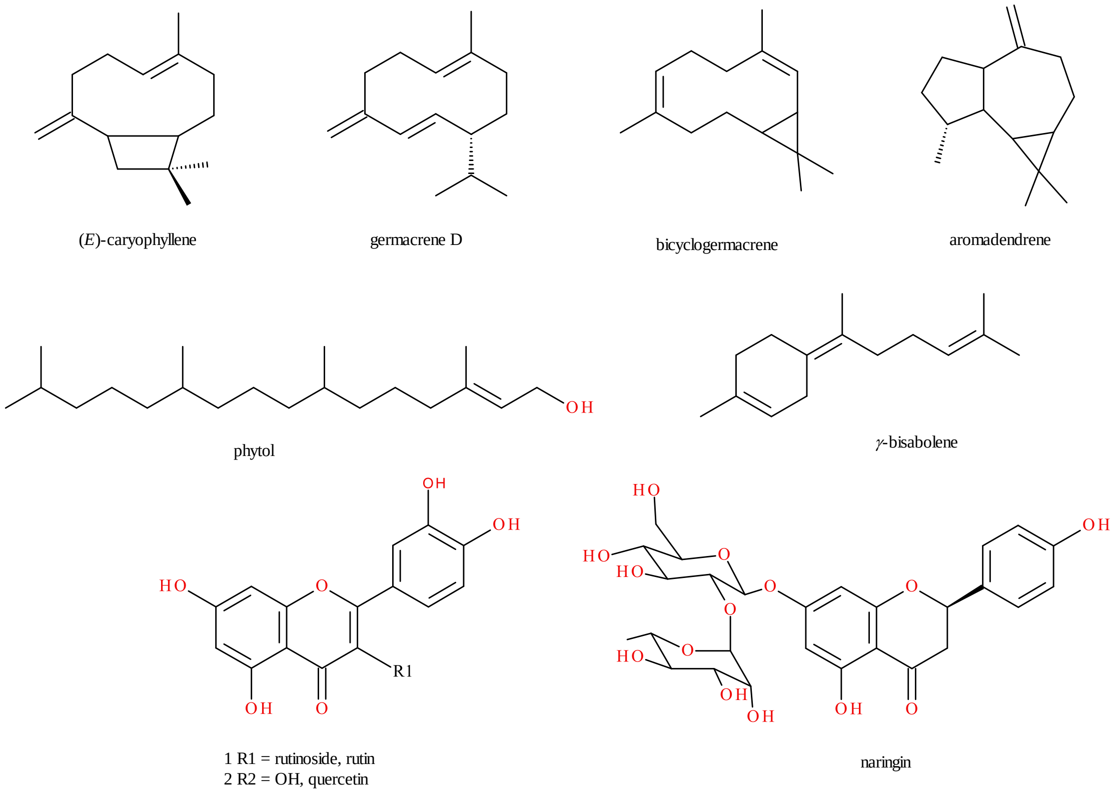


Figure 2: Structures of compounds reported in *Piper umbellatum* L. studies.

3.2 Characteristics of included studies

A total of 161 records were identified across four databases (Figure 3). Title and abstract screening were carried out directly during each database search, yielding 93 potentially relevant studies, which were subsequently imported into Rayyan. Of these, 35 reports were selected for full-text retrieval, and all full texts were successfully accessed. After full-text assessment, six reports were excluded for presenting non-relevant biological activities such as antioxidant effects, antimicrobial activity assessed by diffusion agar method, or inactive results for *Piper umbellatum* L.

A total of 24 articles were included in the study, with Brazil (n = 11) being the primary site for *Piper umbellatum* L. collection, followed by Cameroon (n = 5; Table 1). The most frequently studied plant part was the leaves (n = 16) in both *in vitro* and *in vivo* assays, and the extracts were predominantly polar (n = 12), including hydroalcoholic, ethanolic, or methanolic preparations, which were also associated with the most recently reported biological activities (Table 2). 4-Nerolidylcatechol (4-NC) (Figure 1) was reported as a major chemical constituent in six studies; all conducted in Brazil.

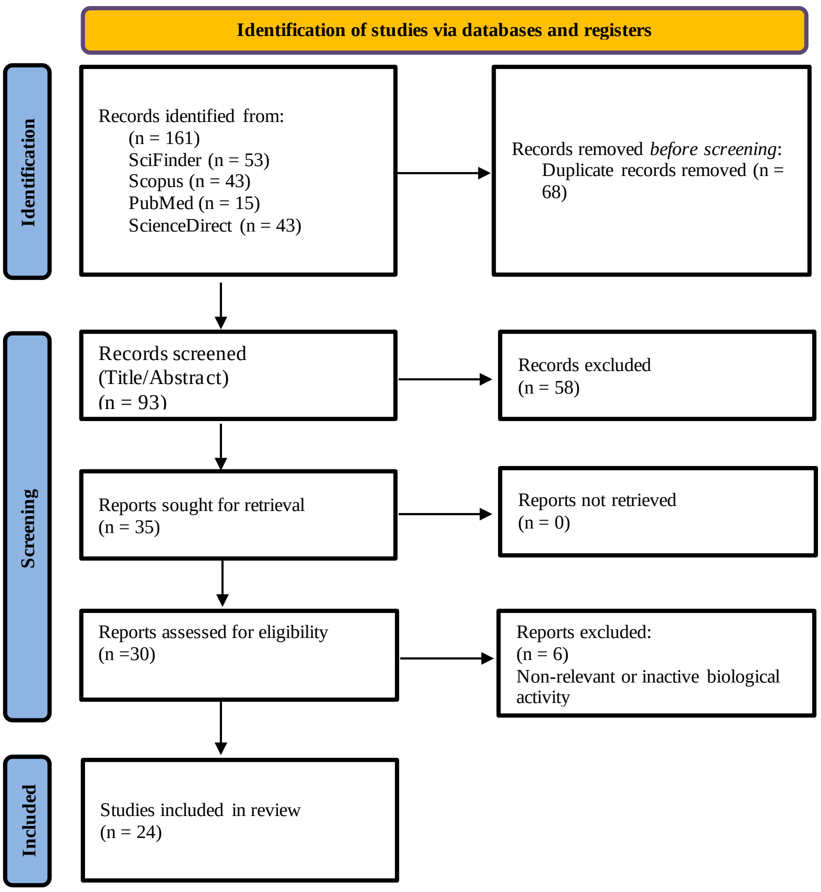


Figure 3: Flowchart of the search process for scientific articles included in the review on *Piper umbellatum* L.

A total of twelve *in vitro* pharmacological activities were identified. For several of them, including antifungal, antischistosomal, cytotoxic, and inhibition of inflammation-related enzymes, activity was observed both in crude extracts and in the isolated compound 4-nerolidylcatechol (4-NC), obtained from hydroalcoholic or ethanolic extracts. The remaining activities, including inhibition of diabetes-related enzymes, filaricidal and microfilaricidal effects, as well as herbicidal, insecticidal, and larvicidal activities, were reported exclusively for crude extracts. Regarding *in vivo* studies, seven activities were reported. Among these, antischistosomal and antitumor effects were demonstrated both in crude extracts and in 4-NC as an isolated compound, while the other activities, anti-inflammatory, gastroprotective and colitis-protective effects, and benefits for sexual and reproductive health, were observed only for crude extracts (Table 2).

Table 2: Summary of *in vitro* and *in vivo* effects of *Piper umbellatum* L. extracts and 4-nerolidylcatechol according to collection site, plant part and extract type studied.

Collection site	Part of plant	Extracts or compound	*In vitro* effects	*In vivo* effects	Reference
Minas Gerais, Brazil	Roots	Hydroalcoholic and hexane extracts, and isolated 4-Nerolidylcatechol (4-NC) from hexane extract	Antischistosomal	Antischistosomal activity of 4-NC (murine models)	Costa *et al.*, 2023
Osun, Nigeria	Seeds	Essential oil	Herbicidal	n.a.	Awojide *et al.*, 2022
Rondônia, Brazil	Leaves	Hydroalcoholic extract	Inseticidal	n.a.	Soares *et al.*, 2022
Oaxaca, Mexico	Leaves	Ethanol and hexane extracts	Larvicidal	n.a.	Jiménez-Durán *et al.*, 2021
Mato Grosso, Brazil	Leaves	Ethanol extract	n.a.	Colonic protection in rats (ulcerative colitis model)	Arunachalam *et al.*, 2020
São Paulo, SP, Brazil	Leaves	4-NC isolated from hydroalcoholic extract	n.a.	Antitumour activity of 4-NC	Alves-Fernandes *et al.*, 2020
São Paulo, Brazil	Leaves	Ethanol extract, and 4-NC isolated from ethanol extract	Antifungal	n.a.	Freitas *et al.*, 2020
São Paulo, SP, Brazil	Roots	4-NC isolated from ethanol extract	Cytotoxic	n.a.	Alves-Fernandes *et al.*, 2019

Yakassé-mé, Côte d'Ivoire	Leaves	Aqueous extract	n.a.	No toxicity in rats (acute toxicity model)	Kanga *et al.*, 2019
Cameroon	Leaves	Methylene chloride/methanol or 70% ethanol	Inhibit the growth and adhesion of the *H. pylor*i	n.a.	Ngnameko *et al.*, 2019
Bazou, Cameroon	Leaves	Methanol Extract	Inhibition of diabetes-related enzymes	n.a.	Njateng *et al.*, 2018
Obala, Cameroon	Leaves	Aqueous Extract	n.a.	Reproductive protection in male rats (libido test)	Francine *et al.*, 2017
-	Roots	4-NC isolated from hidroethanolic extract	Cytotoxicity	n.a.	Massaro *et al.*, 2017
Osun, Nigeria.	Seeds	Essential oil	Anti-termitic	n.a.	Awojide; Lajide; Owolabi, 2016
Cameroon	Leaves, Roots, Seeds	Hexane, methylene chloride and methanol extracts	Filaricidal, microfilaricidal, and cytotoxicity activities	No signs of acute toxicity in mice (leaves MC, roots and seed Hex extracts)	Cho-Ngwa *et al.*, 2016
Dschang, Cameroon	Leaves, Seeds	Aqueous leaf and seeds	Antifungal	n.a.	Elisabeth *et al.*, 2016
São Paulo, Brazil	Aerial Parts	Dichloromethane fraction, and 4-NC isolated from hydroethanolic extract	Inhibition of inflammation-related enzymes	n.a.	Lopes *et al.*, 2016
Mato Grosso, Brazil	Leaves	Hydroethanolic extract	n.a.	Gastric protection in mice (ulcer model)	Silva Junior *et al.*, 2016
São Paulo, Brazil	Leaves	Dichloromethane extract	Cytotoxicity	Antitumor activity (Ehrlich model) without acute toxicity, and anti-inflammatory effect (carrageenan-induced edema) in mice	Iwamoto *et al.*, 2015
Mato Grosso, Brazil	Leaves	Essential oil	Insecticidal	n.a.	Pauliquevis *et al.*, 2015
São Paulo, Brazil,	Aerial parts	Ethyl-acetate fraction	Antibacterial activity in a root canal model	n.a.	Sponchiado Júnior *et al.*, 2014

Veracruz, Mexico	Leaves	Ethanol extract	Insecticidal	n.a.	Carmona-Hernández *et al.*, 2014
-	Seeds	Ethanol extract	Bactericidal	n.a.	Ejele *et al.*, 2014
Mato Grosso, Brazil	Leaves	Hydroethanolic extract	Antibacterial	No toxicity in mice (acute model)	Silva Jr *et al.*, 2014

Legend: n.a.: not available; the article did not report data for this activity in the corresponding *in vitro* or *in vivo* assays.

3.3 Antidiabetic (inhibitor) effects

Recently, the traditional use of *Piper umbellatum* L. in Cameroon for diabetes management was evaluated for its inhibitory activity against enzymes associated with glycemic regulation. The methanolic extract of *P. umbellatum* showed inhibition of *α*-glucosidase (IC_{50} = 16.71 ± 1.42 µg/mL) and maltase-glucoamylase (IC_{50} = 31.77 ± 1.17 µg/mL). In contrast, it exhibited low inhibition against *β*-glucosidase (15.33 ± 0.81% at 100 µg/mL), indicating selectivity toward other glucosidases (Njateng *et al*., 2018). In addition, the extract significantly inhibited enzymes that can play important roles in the development of chronic diabetic complications such as aldose reductase (IC_{50} = 6.66 ± 0.12 µg/mL) and aldehyde reductase (IC_{50} = 9.16 ± 0.58 µg/mL), showing greater potency than reference drug such as genistein (IC_{50} = 45.60 ± 2.16 µg/mL) (Njateng *et al*., 2018).

Gas Chromatography–Mass Spectrometry (GC-MS) analysis of the *P. umbellatum* extract revealed the presence of aromatic benzene derivatives, which are structurally related to antidiabetic agents like benzoic acid derivatives used in type 2 diabetes therapy. These findings support the traditional use of *P. umbellatum* in diabetes management and reveal the potential of this medicinal plant as cost-effective sources of enzyme inhibitors acting on metabolic pathways involved in diabetes complications and digestion (Njateng *et al*., 2018).

3.4 Antischistosomal effects

Piper umbellatum L. has also demonstrated promising activity against parasitic infections, including schistosomiasis. Hydroalcoholic and hexane extracts from *P. umbellatum* L. roots were active *in vitro* against *Schistosoma mansoni*, with EC_{50} values below 20 µg/mL, and selectivity indexes greater than 10 against Vero mammalian cells (Costa *et al*., 2023). Although there are no popular reports of *P. umbellatum* being used to treat schistosomiasis, the plant is traditionally employed for liver diseases, fever, as a sudorific, and for intestinal disorders, as identified by Roersch (2010). 4-NC, a compound isolated from its hydroethanolic extract, exhibited a more effective EC_{50} value (0.91 µg/mL;2.9 µM) than crude extracts and showed low cytotoxicity (CC_{50}>200 µM) in Vero cells, even against *Caenorhabditis elegans* from doses of 50-200 µM. Furthermore, the compound demonstrated moderate *in vivo* therapeutic efficacy against worm burden reduction (52.1%) in murine model of patent *S. mansoni* infection, by oral treatment with a dose of 400 mg/kg, leading to a reduction in egg in feces (52.3%), also in patent (61.7%) and prepatent (43.9%) models as well as in liver and spleen weights (Costa *et al*., 2023).

3.5 Filaricidal and microfilaricidal effects

This medicinal species used in Cameroon to treat onchocerciasis has also been investigated for its activity against filarial parasites such as *Onchocerca ochengi* worms and *Loa loa* which coexist in the same endemic regions of Africa, infecting the same individuals, which complicates onchocerciasis chemotherapy (Cho-Ngwa *et al*., 2016).

Cho-Ngwa *et al.* (2016) identified that extracts of varying polarities from the leaves, roots, and seeds of *Piper umbellatum* L. exhibited activity against both male and female *Onchocerca ochengi* worms, thereby validating its traditional use. Most of these extracts were more active against *O. ochengi* adult females (IC_{50} 35.65-162.70 µg/mL) and males (IC_{50} 16.63-48.89 µg/mL) comparison to monkey kidney epithelial cells (LLC-MK2 cells) with values of SI values above 1, and highly active against *Loa loa* microfilariae (IC_{50} 31.25-125.0 µg/mL).

The most potent non-polar extracts from the seeds (PUShex) and roots (PURhex), as well as the dichloromethane extracts from the leaves (PULmc) of *P. umbellatum*, contain sterols and flavonoids according to phytochemical analysis, and showed no signs of toxicity in an acute model using Balb/c mice at the limit dose of 2000 mg/kg body weight, reinforcing the plant's antiparasitic relevance (Cho-Ngwa *et al*., 2016).

3.6 Herbicidal, insecticidal, larvicidal and anti-termitic effects

In addition to its therapeutic applications in humans, *Piper umbellatum* L. has also shown significant bioactivity against agricultural pests and disease vectors. The essential oil of *P. umbellatum* seeds exhibited herbicidal activity by inhibiting the growth of the shoot and root, as well as phytotoxic activity on *Vigna unguiculata* L., *Solanum lycopersicum* L., and *Zea mays* L.. Sesquiterpenes such as caryophyllene (10.44%), aromadendrene (13.74%), and γ-bisabolene (8.06%) (Figure 2) were identified by GC-MS as the major components (Awojide *et al*., 2022). On the other hand, fatty acids were identified as the main components in leaves extracted with both hexane and ethanol, with a predominance of sesquiterpenes in the hexane extract (Jiménez-Durán *et al*., 2021).

The insecticidal properties of polar extracts from leaves and aerial parts, as well as the essential oil from the leaves have also been reported against *Sitophilus zeamais* (maize weevil) by surface contact exposition, on *Drosophila melanogaster* adults by disk assay contact, and *Hypothenemus hampei* by topical treatment assay (coffee borer beetle) (Soares *et al*., 2022; Pauliquevis *et al*., 2015; Carmona-Hernández *et al*., 2014).

Additionally, larvicidal activity against *Spodoptera frugiperda* (J.E. Smith), a voracious larvae crop for corn, has been reported for ethanol extract (LC_{50} 92-184 $\mu g/cm^2$) from dehydrated and fresh leaves of *P. umbellatum* collected in Mexico. The ethanol extract from the dehydrated leaves showed the presence of fatty acids diterpene phytol (Figure 2), and aldehyde as major components by CG-MS analysis (Jiménez-Durán *et al*., 2021).

Termiticidal agents from natural sources are especially important for the protection of wood and other materials in remote areas and among low-income populations in Africa. The essential oils from *P. umbellatum* seeds were also effective against *Macrotermes subhyalinus* in contact assays (EC_{50} of 0.596 mL/L) and repellence assays (EC_{50} of 0.809 mL/L), and GC-MS analysis suggest that its anti-termitic activity may be attributed to the presence of sesquiterpenes and monoterpenes (Awojide *et al*., 2022).

3.7 Antimicrobial effects

The plant has exhibited a broad spectrum of antimicrobial activity, reinforcing its therapeutic versatility and relevance in the context of bacterial and fungal infectious diseases, including wound and skin diseases, and respiratory tract conditions. The crude ethanol extract from the leaves of this medicinal plant, unlike its aqueous and hexane counterparts, exhibited antifungal activity against *Trichophyton rubrum* (MIC 156.3 mg/mL) and *Microsporum canis* (MIC 39.1 mg/mL), without cytotoxic effects against a human lung non-tumoral cell line (MRC-5; IC_{50} of 100.2 μM) and human liver tumoral cell line (HepG2; IC_{50} of 58.2 μM). These dermatophyte fungi invade human keratinized tissues, and their eradication generally demands long-term treatment. The compound 4-

nerolidylcatechol (4-NC), a phenolic meroterpene, was isolated as the bioactive constituent responsible for the antifungal activity by bioassay-guided study, showing minimum inhibitory concentration (MIC) values against *Trichophyton rubrum* (MIC 4.9 μM) and *Microsporum canis* (MIC 2.4 μM) comparable to those of terbinafine and griseofulvin. However, selective index (SI >10) was observed only against *M. canis* (Freitas *et al*., 2020).

In contrast, aqueous extracts from the same plant part, as well as from the seeds, also demonstrated antifungal activity against *Candida albicans* (MIC 40 mg/mL and MIC 10 mg/mL) and *Candida glabrata* (MIC 5 mg/mL and MIC 40 mg/mL) from patients with vaginal candidiasis using the microbroth dilution method, although some authors have considered these MIC values to be relatively high (Elisabeth *et al*., 2016; Cos *et al*., 2006).

Meanwhile, the antibacterial activity of the ethyl acetate fraction derived from the aerial parts of *Piper umbellatum* L. was effective to reducing *Enterococcus faecalis* (ATCC 29210) when applied as an intracanal medication in a root canal contamination model using human maxillary canine teeth. Its inhibitory activity against the microbiota resistant to conventional endodontic treatment suggests that this species is quite promising as phytotherapeutic agent (Sponchiado Júnior *et al*., 2014). Moreover, these findings support earlier results for the hydroethanolic extract (HEPu), which showed activity not only against *E. faecalis*, but also against others Gram-negative microorganisms including *Klebsiella pneumoniae*, *Salmonella typhimurium*, and *Shigella flexneri*, with MIC values ranging from 12.5 to 25 µg/mL, and without cytotoxicity in Chinese hamster ovary (IC_{50} > 200 µg/mL). Studies about its mode of antibacterial action showed that HEPu increases the permeability of bacterial cytoplasmic membranes of *Shigella flexneri*, can provoke K^+ efflux and nucleotide leakage in from *E. faecalis* and *S. flexneri*. The presence of flavonoids in the extract by high performance liquid chromatography analysis, especially rutin and quercetin (Figure 2), was associated with changes in the permeability of cell wall (Silva Jr *et al*., 2014).

Furthermore, the ethanol extract and its acidic metabolite from the seeds exhibited antibacterial effects against *Coliform bacilli*, *Salmonella typhi*, and *Staphylococcus aureus* by the agar disc diffusion method. Naringin (Figure 2), a flavonoid isolated from the active acidic fraction was suggested to be antimicrobial agent of the plant (Ejele *et al*., 2014).

3.8 Gastric and colitis protection effects

The therapeutic relevance of *Piper umbellatum* L. extends to the gastrointestinal system, where preclinical studies have supported its traditional use for treating gastric and intestinal disorders. Protective medicinal properties for the gastrointestinal system of this species have been demonstrated in mammals, particularly for ethanol leaf extracts (HEPu), in mouse model of induced gastric ulcers and in ulcerative colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) in rats, with both studies employing equal oral doses. HEPu also reduced gastric and colonic lesions and ulcerated area in both models by more than 50% at a dose of 300 mg/kg body weight (Arunachalam *et al*., 2020; Silva Junior *et al*., 2016).

Its effectiveness in treating gastritis, supporting its traditional use in the Brazilian Amazon, was accompanied by its antisecretory and anti-inflammatory effects. Additionally, it positively modulates antioxidant defenses related to the activities of superoxide dismutase, myeloperoxidase, and catalase in both gastric ulcer and ulcerative colitis models and immunomodulatory effect by inhibiting the levels of pro-inflammatory markers, including TNF-α, and IL-1β (Arunachalam *et al*., 2020; Silva Junior *et al*., 2016). Although the polar extract demonstrated activity in gastric models, the hydroethanolic extract from leaves was not able to inhibit *Helicobacter pylori* at concentrations ranging from 3.25 to 400 µg/mL. This finding was consistent anti-adherence effect of the leaf extract in a high dose (20 mg/mL) in assays conducted by Ngnameko *et al*. (2019), suggesting that such an effect might not be detected at lower concentrations, such as 400 µg/mL.

Its therapeutic action in colitis corroborated popular use for as intestinal pain in Congo (Roersch, 2010; Corrêa, 1909) was further evidenced not only by the reduction in lesions, also by preservation of the epithelial barrier, maintenance of crypt numbers, increased goblet cell presence, and reduced submucosal edema, which was confirmed by enhanced mucin secretion (Arunachalam *et al*., 2020).

3.9 Cytotoxic, antitumor and anti-inflammatory effects

Although no traditional use of *Piper umbellatum* L. specifically refers to cancer treatment, the plant has been employed for "inflamed tumors" in ethnobotanical records (Roersch, 2010). Interestingly, both *in vitro* and *in vivo* studies have demonstrated its cytotoxic and antitumor properties, suggesting that these traditional uses may reflect empirical recognition of its potential in oncological contexts.

The *in vitro* antiproliferative activity of the *P. umbellatum* dichloromethane (DCM) leaf extract against a panel of mammalian cancer cell lines has been reported, and this effect was also demonstrated by purified 4-nerolidylcatechol (4-NC), isolated from hydroalcoholic or ethanolic extracts depending on the study (Alves-Fernandes *et al.*, 2020; 2019; Massaro *et al.*, 2017; Iwamoto *et al.*, 2015). In general, *in vitro* studies demonstrate selective cytotoxic effects on tumor cells compared to normal cells (Costa *et al.*, 2023; Cho-Ngwa *et al.*, 2016; Iwamoto *et al.*, 2015; Silva Jr *et al.*, 2014). *In vitro* assays, the isolated compound 4-NC also displayed activity against glioblastoma cells by inducing autophagy pathway and cutaneous melanoma including against naïve, resistant and double-resistant cells (Massaro *et al.*, 2017). It also inhibited colony formation and decreased invasiveness of drug-resistant cells in two and three-dimensional cell culture models with apoptosis induction by endoplasmatic reticulum stress activation and partially dependent on CHOP (C/EBP homologous protein, also known as GADD153), a key mediator of ER stress-induced apoptosis (Alves-Fernandes *et al.*, 2019).

Both the dichloromethane leaf extract and 4-NC have demonstrated tumor-reducing effects in mouse models (Alves-Fernandes *et al.*, 2020; Iwamoto *et al.*, 2015). The DCM extract (100, 200, and 400 mg/kg) was considered non-toxic in a murine subchronic toxicity model, with no hematological alterations observed. It also showed anti-inflammatory effects in the carrageenan-induced paw edema model, further supported by its ability to inhibit nuclear factor kappa B (Lopes *et al.*, 2016).

Corroborating these findings, acute toxicity studies with an aqueous leaf extract of *P. umbellatum* in rats suggest an LD_{50} above 5000 mg/kg. Subacute studies indicated a decrease in weight gain and triglyceride levels in female rats, and a reduction in creatinine levels in male rats (Kanga *et al.*, 2019).

More recent findings have further characterized the effects of the isolated compound 4-NC, which reduced tumor growth in *in vivo* models without inducing systemic toxicity. Interestingly, it also modulated immune responses, particularly by reducing lymphocyte counts in bone marrow, an effect possibly associated with its anti-inflammatory activity (Alves-Fernandes *et al.*, 2019). Taken together, these results not only reinforce the antitumor potential of *P. umbellatum* and its isolated compound 4-NC, but also consistently support their anti-inflammatory activity across different models, from classical inflammation assays to immunomodulatory effects at the cellular level.

3.10 Sexual and reproductive health effects

While *Piper umbellatum* L. has been historically employed in female reproductive contexts, such as postpartum care and menstruation regulation, as well as in the treatment of female infertility, its role in supporting male fertility and sexual activity has not been reported in ethnobotanical literature (Francine *et al*., 2017; Roersch, 2010).

Aqueous extracts of leaves have shown protective effects on the male reproductive system in rats following oral administration (75 and 150 mg/kg body weight) for 60 days, including improvements in testicular and epididymal weight, sperm quality parameters (count, motility, and viability), and antioxidant enzyme activity (Francine *et al*., 2017). These effects were observed in a model of aluminium-induced reproductive toxicity and suggest that *P. umbellatum* may support male reproductive function by mitigating oxidative stress and enhancing testicular protein synthesis. These findings suggest an expansion of its therapeutic potential beyond culturally documented uses.

3.11 Convergence between pharmacological evidence and traditional uses

Figure 3 provides a summary overview of the findings from this review. It also highlights as most newly reported *in vitro* activities over the past decade, such as antibacterial (new targets), antischistosomal, inhibition of enzymes related to anti-inflammatory effects (cyclooxygenase-2 inhibition) and diabetes (maltase, glucosidases, aldose reductase), and for filaricidal and microfilaricidal actions, as well as effects on non-human targets, including anti-termite, herbicidal, insecticidal, larvicidal activities. In contrast, *in vivo* studies published since 2014 have reported antischistosomal effects, gastric antisecretory activity, protection against colitis and gastric lesions, and sexual and reproductive protective effects.

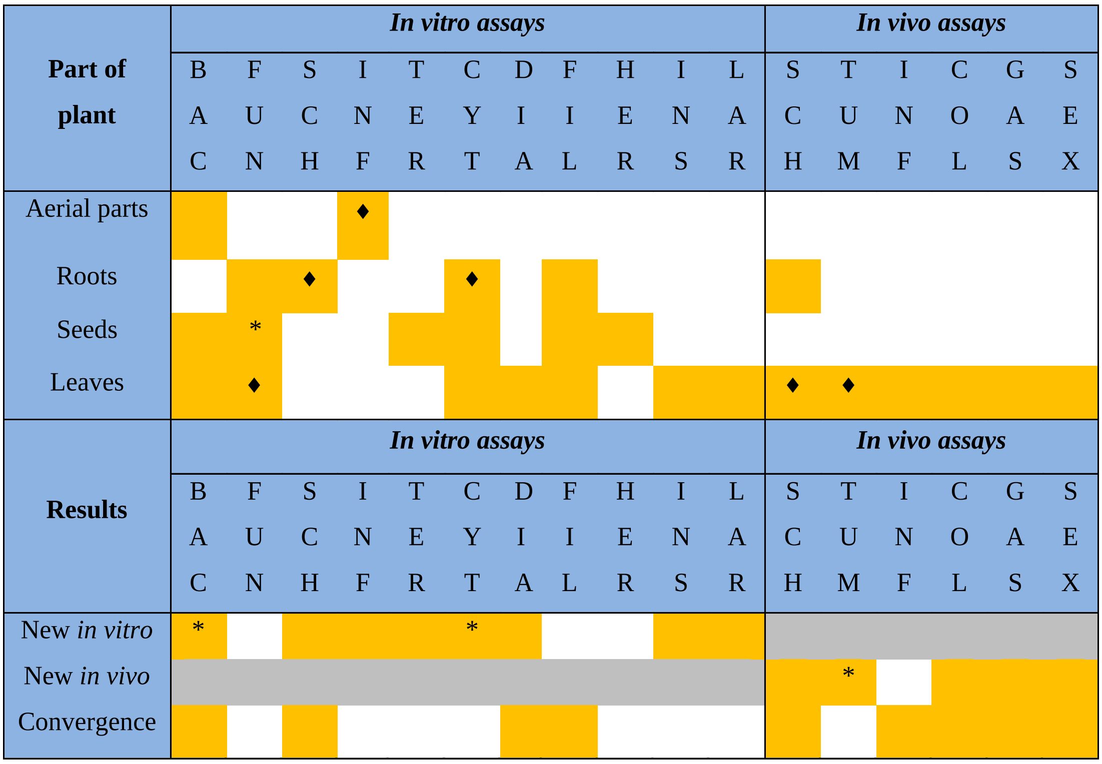
Although 4-nerolidylcatechol (4-NC) has been identified as a prominent bioactive compound in *Piper umbellatum* L. for antischistosomal, antifungal, anti-inflammatory, cytotoxic, and antitumour effect, comprehensive pharmacological investigations considering other constituents seems to remain limited (Costa *et al*., 2023; Alves-Fernandes *et al*., 2020; 2019; Freitas *et al*., 2020; Massaro *et al*., 2017; Lopes *et al*., 2016).

While 4-NC has been associated with various activities, the pharmacological potential of the broader array of secondary metabolites in this species remains largely unexplored.

Taken together, the pharmacological findings discussed throughout this review reveal a meaningful convergence with the traditional uses of *P. umbellatum*, highlighting its relevance as both a culturally embedded and scientifically supported medicinal plant (Figure 3) (Roersch, 2010). Traditional applications for treating infectious conditions such as erysipelas, abscesses, and sexually transmitted infections align with demonstrated antibacterial activity. Likewise, its historical use against fever, liver ailments, and intestinal parasites finds support in studies reporting antischistosomal effects. The antidiabetic potential corroborates its use in folk medicine for managing diabetes. Experimental data showing colonic and gastric protection reinforce its role in treating digestive disturbances like diarrhea, dyspepsia, and ulcers. Furthermore, anti-inflammatory properties reflect widespread traditional use for swellings, bruises, and inflamed tissues. Finally, its popular use as an aphrodisiac is consistent with recent evidence of effects on sexual and reproductive health.

This convergence is also reflected in Brazilian traditional medicine, where *P. umbellatum* is used to treat skin diseases, syphilis, gonorrhea, diarrhea, filariasis, liver disorders, muscular pain, inflammation, swellings, and contusions (SiBBr, 2025). These parallels reinforce its therapeutic value and underscore the importance of further scientific validation.

Despite the growing number of pharmacological studies on *P. umbellatum*, this review highlights important gaps in current knowledge. First, the mechanisms of action underlying the biological activities reported for crude extracts remain poorly investigated, limiting a deeper understanding of their therapeutic potential. Second, none of the evaluated studies used chemically standardized extracts, which hinders comparison of results and compromises the reproducibility of findings. Third, no clinical trials involving *P. umbellatum* were found among the 24 selected studies, nor in complementary searches in the PubMed and SciFinder®l databases, indicating a lack of translational research. Finally, although crude extracts are generally considered safe in preclinical models, subacute toxicity studies remain scarce, and broader toxicological evaluations would be essential to support their potential use in phytotherapeutic formulations including genotoxicity, mutagenicity, embryotoxicity, and teratogenicity assays.



Activity observed in experimental assays.

No one activity observed in selected studies published between 2014–2024.

Not applicable to assay type.

Figure 3: Mapping of biological activities of *Piper umbellatum* L. extracts and 4-nerolidylcatechol by plant part and experimental model *(in vitro/in vivo*), highlighting new effects and convergence with traditional uses.

Legend: BAC: antibacterial effect, FUN: antifungal effect, SCH: antischistosomal effect, INF: anti-inflammatory effect, TER: anti-termitic effect, CYT: cytotoxic effect, DIA: antidiabetic effect, FIL: filaricidal/microfilaricidal effect, HER: herbicidal effect, INS: insecticidal effect, LAR: larvicidal effect, TUM: antitumour effect, COL: colitis protection effect, GAS: gastric protection effect, SEX: sexual and reproductive health effects; ♦: 4-Nerolidylcatechol was also active in the assay. *The extracts were tested against new targets (2014-2024) comparison data published by Roersch (2010). Convergence between biological activity and traditional use reported by Roersch (2010): **Antibacterial:** treatment of antiseptic conditions (leaf), erysipelas (leaf, root), abscesses (leaf, root), boils (leaf, root), syphilis (leaf, root), and gonorrhea (leaf, root); **Antischistosomal:** used for liver conditions (root), fever and as a febrifuge (leaf, root), and intestinal parasites (leaf, whole plant); **Anti-inflammatory (enzymatic activity):** indicated for general inflammation (leaf, root), swellings (leaf), contusions and bruises (leaf), leg inflammation, and inflamed tumors (leaf, root); **Gastric protective:** employed for digestive issues (root), dyspepsia (root), peptic ulcers (leaf), stomach edema (leaf), and stomachaches (leaf, root); **Colitis protection:** associated with diarrhea (leaf, root), constipation (root), dysentery (leaf), bloody diarrhea (leaf), and abdominal pain (root); **Sexual and reproductive health:** used as an aphrodisiac (root) and for infertility (root); **Diabetes (enzymatic activity):** traditionally used in the treatment of diabetes (leaf).

4. CONCLUSION

Piper umbellatum L. exhibits a wide range of promising pharmacological activities in both human and non-human models, with growing evidence aligning with its traditional uses. Notably, antibacterial, antischistosomal (hepatic), antidiabetic, gastric, and colonic protective effects, as well as modulation of inflammatory and reproductive markers, have been experimentally demonstrated. These findings strengthen the rationale for its use in treating infections, gastrointestinal disorders, and inflammatory conditions, commonly addressed by traditional medicine in Brazil. Given its therapeutic potential, further research is warranted, including studies on mechanisms of action, chemical standardization, comprehensive toxicological assessments, and rigorously designed clinical trials.

In addition to these experimental advances, it may also be valuable to perform bibliometric and patentometric analyses capable of mapping the scientometric evolution of studies on *P. umbellatum*. Such analyses can help identify technological trends, knowledge gaps, and opportunities for innovation in the pharmaceutical field. Furthermore, considering the growing body of chemical and pharmacological evidence validating its traditional uses, future discussions could address the potential reintegration of *P. umbellatum* into the Brazilian Pharmacopoeia. This would require progress in areas such as herbal drug standardization, safety-focused toxicological studies, and well-designed clinical trials, all of which are essential steps toward supporting regulatory processes and the formal recognition of the species as a safe and effective therapeutic resource.

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AUTHORSHIP CONTRIBUTION

Betania Barros Cota: Conception and design of the study; literature review; data collection and analysis; preparation of tables; initial drafting of the manuscript; critical revision of the intellectual content.

Ana Clara Romualdo: support in data collection, critical revision, and approval of the final version for submission.