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Article

Therapeutic and Biotechnological Potential of Passiflora Incarnata: An Integrative Review

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ABSTRACT
Passiflora incarnata L., known as purple passionflower, has broad therapeutic potential and is traditionally used in the treatment of insomnia, anxiety, and other conditions related to the central nervous system. The present study conducted an integrative review to characterize the main bioactive compounds of the species, their mechanisms of action, pharmacological applications, possible drug–drug interactions, and to assess their biotechnological and regulatory feasibility. The methodology involved the analysis of scientific publications from, collected from databases such as PubMed, Virtual Health Library (VHL), SciELO, Science Direct, and Web of Science, with an emphasis on phytochemical studies, clinical trials, Brazilian Pharmacopoeia protocols, and ANVISA guidelines. The results indicated that flavonoids (such as vitexin and isovitexin) and β-carboline alkaloids (harmine and harmaline) are primarily associated with the plant's anxiolytic and sedative actions, via GABAergic modulation and MAO-A inhibition. Biotechnological methods such as in vitro cultivation, micropropagation, supercritical CO_2 extraction, and nanoencapsulation were identified as sustainable and effective alternatives for standardizing extracts. The study also highlighted the need for strict quality and safety control for the registration of herbal medicines with the Brazilian Health Regulatory Agency (ANVISA). It is concluded that *P. incarnata* may have a promising profile for clinical and industrial use, provided that technical-scientific criteria and regulatory requirements are respected, with research and environmental conservation being essential to ensure sustainable exploitation.
Keywords: anxiety; biotechnology; *Passiflora incarnata*; phytotherapy; quality control.

RESUMO
A *Passiflora incarnata* L., conhecida como maracujá-roxo, tem amplo potencial terapêutico e é tradicionalmente utilizada no tratamento da insônia, ansiedade e outras condições relacionadas ao sistema nervoso central. O presente estudo realizou uma revisão integrativa para caracterizar os principais compostos bioativos da espécie, seus mecanismos de ação, aplicações farmacológicas, possíveis interações medicamentosas e avaliar sua viabilidade biotecnológica e regulatória. A metodologia envolveu a análise de publicações científicas, coletadas de bases de dados como PubMed, Biblioteca Virtual em Saúde (BVS), SciELO, Science Direct e Web of Science, com ênfase em estudos fitoquímicos, ensaios clínicos, protocolos da Farmacopeia Brasileira e diretrizes da ANVISA. Os resultados indicaram que os flavonoides (como vitexina e isovitexina) e os alcaloides β-carbolínicos (harmina e harmalina) estão principalmente associados às ações ansiolíticas e sedativas da planta, por meio da modulação GABAérgica e da inibição da MAO-A. Métodos biotecnológicos, como cultivo in vitro, micropropagação, extração supercrítica de CO_2 e nanoencapsulação, foram identificados como alternativas sustentáveis e eficazes para padronizar extratos. O estudo também destacou a necessidade de um rigoroso controle de

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qualidade e segurança para o registro de medicamentos fitoterápicos na Agência Nacional de Vigilância Sanitária (ANVISA). Conclui-se que a *P. incarnata* pode ter um perfil promissor para uso clínico e industrial, desde que os critérios técnico-científicos e os requisitos regulatórios sejam respeitados, sendo a pesquisa e a conservação ambientais essenciais para garantir a exploração sustentável.
Palavras-chave: ansiedade; biotecnologia; *Passiflora incarnata*; fitoterapia; controle de qualidade.

Introduction

Passiflora incarnata L., commonly known as purple passionflower, is a climbing plant belonging to the Passifloraceae family, widely distributed in tropical and subtropical regions, associated primarily with the temperate biome. Interest in *P. incarnata* has increased in both traditional medicine and modern pharmacology due to its therapeutic potential and diverse phytochemical profile (Gilbert *et al.*, 2022; Wohlmuth *et al.*, 2010).

Evidence suggests that *P. incarnata* is traditionally used as a natural calming agent and for the treatment of sleep and anxiety disorders. These traditional uses are supported by preclinical and clinical studies, although the overall certainty of evidence remains moderate (Sinnott-Armstrong *et al.*, 2022) . Recent studies identify flavonoids and β-carboline alkaloids (e.g., harmine, harmaline) as key contributors to its CNS effects, primarily via positive modulation of GABA_A receptors and MAO-A inhibition (Madavi *et al.*, 2024).

Among the pharmacological properties of *P. incarnata*, its calming effects and a series of additional effects that have been the subject of study stand out. As demonstrated in several studies, the analgesic and anti-inflammatory activity of the compound is attributed to the presence of phenolic compounds and flavonoids, which act to inhibit inflammatory mediators such as prostaglandins (Miroddi *et al.*, 2013).

This calming effect broadens the spectrum of use, not limited to adjunctive use in cases of anxiety, but also extending to the relief of chronic pain and inflammatory conditions of musculoskeletal origin, such as arthritis and myalgia. Other laboratory studies have shown that the plant has significant antioxidant activity, protecting cells against oxidative stress, a factor involved in the genesis of neurodegenerative, cardiovascular, and oncological diseases(Ferreira *et al.*, 2022; Willian & Pereira, 2017).

In the field of biotechnology, the species has been the subject of research for crop optimization, production of secondary metabolites in bioreactors, and obtaining standardized extracts, with the aim of ensuring quality, efficacy, and pharmacotechnical safety. The feasibility of its use in pharmaceutical formulations, such as capsules, tinctures, and fluid extracts, has been evaluated according to the criteria established by the Brazilian Pharmacopoeia. This reinforces its potential for inclusion in the herbal medicine market (Yesenia Solís-Ramos *et al.*, 2013).

Its high degree of ecological adaptability and hardiness give *P. incarnata* the ability to be easily cultivated in agroecological systems, promoting sustainable production and the appreciation of native Brazilian species in the natural medicine production chain (Bortoluzzi *et al.*, 2020; Lyca R. da Fonseca *et a*l., 2020).In this context, it is important to note that the conventional use of the plant has been crucial in guiding contemporary research, establishing a successful example of integration between popular knowledge and science(Amini et al., 2023). The broad knowledge about the safe use of *P. incarnata*, combined with robust pharmacological research, provides support for its incorporation into evidence-based health practices, notably in the field of integrative phytotherapy recommended by the Brazilian Unified Health System (UHS). The scientific validation of its therapeutic application contributes to the advancement of public policies aimed at promoting health through natural, sustainable, and accessible resources.

According to the data presented, the choice of. *P. incarnata* as a subject of study is justified not only by its proven therapeutic properties, but also by its potential to foster the development of innovative, sustainable, and economically viable herbal medicines, especially in countries with high biodiversity, such as Brazil (Wang *et al.*, 2021). Given that *Passiflora incarnata* is not a native species of Brazil, encouraging the cultivation and use of native species of the genus Passiflora, including wild Brazilian passionflowers, can contribute to the conservation of biodiversity, the generation of income in local communities, and the enhancement of plant genetic resources (Otoni *et al.*, 2024).

Considering the above, this study aims to characterize the chemical composition, pharmacological actions, clinical studies, and biotechnological applications of *P. incarnata*, emphasizing its viability for pharmaceutical use according to the quality, efficacy, and safety standards established by the Brazilian Pharmacopoeia. The proposal also aims to promote knowledge about this medicinal plant and contribute to the development of strategies that integrate science, health, and sustainability, in line with the principles of traditional medicine, scientific innovation, and biodiversity conservation.

Although previous reviews have addressed the phytochemical composition, pharmacological properties, and clinical applications of *P. incarnata*, the relationship between the characterization of the preparations used in the studies and the observed results remains largely unexplored. Differences in the plant part used, extraction

methods, solvents, concentrations, doses, and chemical markers make it difficult to compare findings and interpret pharmacological and clinical effects. This review, therefore, stands out by integrating these characteristics of the preparations with the available therapeutic evidence, seeking to identify how the variability of the extracts may be related to the results reported for *P. incarnata*.

Materials and Methods

This study is characterized as an integrative literature review, a method that allows for the compilation and synthesis of results from studies with different designs (Lubbe; Ham-Baloyi; Smit, 2020). This approach was adopted to integrate evidence on the phytochemical composition, pharmacological effects, safety, biotechnological applications, and regulatory aspects of *P. incarnata*. The review was conducted in six stages: definition of the research question, literature search, study selection, data extraction, analysis, and synthesis of results.

Research Question

The research question was structured based on the PCC strategy, comprising Population, Concept, and Context. The guiding question was: What scientific evidence is available regarding the chemical composition, pharmacological properties, safety, biotechnological applications, and regulatory aspects related to *P. incarnata*?

In the Population (P) component, the species *Passiflora incarnata* L. was considered, including extracts, preparations, and derived compounds. The Concept (C) encompassed phytochemical composition, pharmacological activities, mechanisms of action, efficacy, toxicity, safety, drug interactions, and biotechnological processes. The Context (C) included experimental, preclinical, and clinical studies, as well as pharmaceutical applications, standardization, quality control, and regulatory aspects related to the use of the species.

Search Strategy

The literature search was conducted between July and August 2025 in the MEDLINE/PubMed, Virtual Health Library (VHL), SciELO, ScienceDirect, and Web of Science databases, with no restrictions on the year of publication.The search terms were organized into three conceptual groups. The first group comprised terms related to the species: "*Passiflora incarnata*," "purple passionflower," and "passionflower." The second group included terms referring to phytochemical, pharmacological, and therapeutic aspects: "pharmacological activity," "therapeutic activity," pharmacology, phytochemistry," bioactive compouds," anxiety, anxiolytic, insomnia, sleep, toxicity, safety and "drug interaction." The third block covered terms related to biotechnology, standardization, and quality control: biotechnology, extraction, "*in vitro* culture," micropropagation, nanoencapsulation, standardization, "quality control," phytotherapy, and "herbal medicine." Within each block, the terms were combined using the Boolean operator OR, while the combination across blocks followed the structure (#1) AND (#2 OR #3), with adaptations to the syntax of each database.

Eligibility Criteria

Studies were included that directly investigated *P. incarnata* and presented results related to phytochemical composition, pharmacological activity, mechanisms of action, efficacy, safety, toxicity, drug interactions, biotechnological applications, extraction methods, standardization, or quality control. Experimental, preclinical, and clinical studies were considered. Technical and regulatory documents from the Brazilian Pharmacopoeia and the National Health Surveillance Agency were also used in the analysis of aspects related to the quality, standardization, and regulation of products derived from *P. incarnata*. Duplicate records, publications not directly related to the species, studies focused exclusively on other species of the genus Passiflora without specific results for *P. incarnata*, editorials, letters to the editor, conference abstracts, and studies lacking sufficient information on the outcomes of interest were excluded.

Study Selection and Data Extraction

After retrieving the records, duplicates were removed. The initial selection was based on a review of the titles and abstracts. Studies deemed eligible at this stage were reviewed in full. At the end of the process, 20 articles were included in the synthesis of results. Their main characteristics are presented in picture 1. Data were extracted using a matrix containing authors, year of publication, country, study design, plant part used, characteristics of the preparation or extract, extraction method, solvent, dose or concentration.

1 Picture 1. Characterization of plant material and *Passiflora incarnata* preparations used in the studies.

Author, year	Plant part used	Preparation or extract	Extraction method	Solvent	Plant-to-extract ratio	Chemical standardisation or marker	Concentration or dose
Aman et al., 2016	Aerial parts, without specification of organs	Dry methanolic extract (PI-ME)	Maceration for seven days, filtration and concentration under reduced pressure	Methanol	NI; plant:solvent ratio 1:5 (m/v)	Analysis of flavonoids, alkaloids, saponins and tannins; GC-MS	100–600 mg/kg, depending on the assay
Amini et al., 2023	N/A	Commercial hydroalcoholic extract	N/A	Hydroalcoholic; composition NI	N/A	Total phenolics and flavonoids and antioxidant activity	30, 100 and 300 mg/kg
Azizoğlu et al., 2024	N/A	Commercial *P. incarnata* tablet	N/A	N/A	N/A	N/A	500 mg/kg/day
Blecharz-Klin et al., 2024	Herb; specific organs N/A	Standardised dry extract	Manufacture NI; dissolved in water for administration	Extraction solvent NI; water as vehicle	N/A	Declared as standardised; marker and content NI	30, 100 and 300 mg/kg/day
Boll et al., 2014	N/A	Passiene® commercial herbal syrup	N/A	N/A	N/A	0.19% vitexin	30 and 300 mg/kg/day
Dantas et al., 2017	N/A	Commercial tablet	N/A	N/A	N/A	N/A	260 mg single dose
Deepika et al., 2024a	Mature green leaves	Ethanolic extract (EEP) and liposome-formulated extract (N-EEP)	Drying, pulverisation, sonication for 40 minutes, centrifugation and vacuum concentration	99–99.9% ethanol	NI; plant:solvent ratio 1:15 (m/v)	Phytochemical screening and GC-MS	25–200 µg/mL
Deepika et al., 2024b	Mature green leaves	Ethanolic extract (EEP) and nanoformulated extract (N-EEP)	Drying, pulverisation, sonication, centrifugation and vacuum evaporation	Absolute ethanol	NI; plant:solvent ratio 1:15 (m/v)	Phytochemical screening and GC-MS	In vitro: 25–200 µg/mL; in vivo: 200–2,000 mg/kg
Deepika et al., 2025	Leaves	Ethanolic extract (EEP) and nanoformulated extract (N-EEP)	Sonication, centrifugation and vacuum concentration, as described by Deepika et al. (2024)	Absolute ethanol	NI; plant:solvent ratio 1:15 (m/v)	GC-MS	In vitro: 25–300 µg/mL; in vivo: EEP 300 mg/kg and N-EEP 150 or 300 mg/kg
Dehghani et al., 2025	Dried leaves	Concentrated hydroalcoholic extract	Maceration for 72 hours, vacuum filtration and concentration in a rotary evaporator	96% ethanol and distilled water, in a ratio of 30:70	N/A	N/A	150 mg/kg/day

Deus et al., 2024	N/A	*P. incarnata* capsule combined with *Valeriana officinalis*	N/A	N/A	N/A	N/A	300 mg of *P. incarnata* + 100 mg of *V. officinalis*
Gad et al., 2022	Aerial parts, without specification of organs	Commercial dry extract in capsules	Commercial product; manufacture NI	70% ethanol	N/A	N/A	200 mg/kg/day
Harit et al., 2024	Aerial parts, without specification of organs	Standardised SIVI extract in capsules	N/A	N/A	N/A	Declared as standardised; marker and content NI	600 mg/day
Ożarowski et al., 2018	Dried leaves	Dry methanolic extract	Refluxed for one hour, repeated three times, followed by vacuum concentration	Methanol P.A.	NI; plant:solvent ratio 1:10 (m/v)	HPLC-DAD-MS and LC-MS; C-glycosylated flavonoids and other metabolites	Variable concentrations in cell assays
Sarto et al., 2018	Leaves	Commercial dry extract	N/A	N/A	N/A	0.06% total flavonoids calculated as vitexin	200 mg/kg/day
Schunck et al., 2017	N/A	Commercial dry extract in Sintocalmy® tablets	Tablets pulverised, dissolved in water and filtered	Extraction solvent NI; water as vehicle	N/A	7% total flavonoids, equivalent to 21 mg, expressed as vitexin; free from β-carboline alkaloids	200 mg/kg/day
Kim et al., 2019	Leaves and fruits, in a ratio of 80:20	ethanol extract, concentrated and dried by *spray drying*	Dried, ground material; mixed with the solvent, heated to 80 °C for 2 hours, filtered, concentrated and dried by spray drying	60% ethanol	N/A. The reported ratio of 8:2 corresponds to leaves:fruits, not to the ratio of plant material:extract	Vitexin as the main compound; isovitexin, orientin and isoorientin were also identified by HPLC-UV and LC-MS/MS. The final quantitative content of vitexin in the extract was not clearly stated	DBA/2 mice: 10 and 50 mg/kg/day by gavage for 3 days; memory test: 100 mg/kg/day; SD rats: 2 mg/mL in water; *C. elegans*: 50, 100 and 500 mg/L; cell assay: approximately 0.031–4 mg/mL
Appel et al., 2026	Dried, fragmented or chopped aerial parts	Standardised dry ethanolic extract; 70% native extract, 27% maltodextrin and 3% silicon dioxide	Exhaustive percolation for several hours at 40–50 °C, concentration under reduced pressure, homogenisation and drying	50% (v/v) ethanol	5–7:1	Swertisina and/or isovitexina chemotype; compliance with the *Passiflorae herba* monograph of the European Pharmacopoeia	Graduated concentrations; IC_{50} between 28 and 2,630 µg/mL

Ju et al., 2026	Dried leaves	Freeze-dried crude polyphenol extract (PP)	Ultrasonication at 350 W and 60 °C for 30 minutes; vacuum filtration, evaporation below 50 °C and freeze-drying	70% ethanol	NI; plant:solvent ratio 1 g:25 mL	Yield of 12.1 ± 0.4 per cent; total phenolics of 81.7 mg GAE/g of extract; UHPLC-FT-MS	75 and 150 mg/kg/day
Pandey et al., 2026	Leaves	Ethanolic and aqueous extracts; antimicrobial assay using the ethanolic extract	Dried in the shade and at 35 °C for 24 hours; extraction of 25 g using a Soxhlet apparatus for 18 hours; concentration using a rotary evaporator	Ethanol; aqueous extract also mentioned	N/A; solvent volume not reported	Qualitative screening for alkaloids, glycosides, saponins, phytosterols, flavonoids, phenolics and tannins	Diffusion: 50, 100 and 200 mg; microdilution: 30–120 µg/mL

Source: Prepared by the authors (2026).

Data Analysis and Synthesis

The studies were analyzed descriptively and thematically. Methodological characteristics were considered, as well as, when available, information on the plant part, extraction method, solvent, chemical composition, concentration, and dose (Picture 1). The results were organized into five categories: phytochemical composition and quality control; pharmacological activities and mechanisms of action; clinical efficacy, safety, toxicity, and drug interactions; biotechnological applications and processes for obtaining and standardizing extracts; and regulatory aspects related to the pharmaceutical use of *Passiflora incarnata*. The synthesis compared the studies in terms of the characteristics of the preparations and the results presented, allowing for the identification of differences among the studies and gaps related to standardization, chemical characterization, safety, clinical evidence, and biotechnological applications.

Results

Phytochemical composition and quality control

Phytochemical studies of species in this genus reveal a diversity of volatile compounds, such as esters, terpenes, alcohols, aldehydes, and ketones. The literature cites flavonoids as the major component, accounting for about 2.5% of the phytochemicals present in various plant extracts. These compounds include apigenin, luteolin, quercetin, and kaempferol; anthocyanins are also found in the tissues of various organs of the species. Anthocyanins contribute to the vibrant color patterns of its flowers and to the intense purple color of the fruits of some species. In addition to the compounds mentioned above, most of these species contain flavonoid glycosides, saponins, cyanogenic glycosides, and harmala alkaloids (Casierra-Posada *et al*., 2015) .

P. incarnata. has a rich and diverse chemical composition, with its active ingredients responsible for its widely studied pharmacological effects. Among the main bioactive compounds are flavonoids, alkaloids, phenolic compounds, and complex carbohydrates (Nikolova *et al*., 2024).

Flavonoids are the most studied components and include vitexin, isovitexin, orientin, isoorientin, apigenin, and chrysin. These compounds act mainly on the central nervous system, exerting anxiolytic and sedative effects due to their interaction with GABAergic receptors, a mechanism similar to that of benzodiazepines. Chrysin, in particular, has a modulating action on the GABA system, contributing to the plant's calming effect (Amini *et al*., 2023; Dias *et al*., 2023).

β-carboline alkaloids (e.g., harmine, harmol, and harmaline) have neuromodulatory activities, influencing neurotransmitters such as serotonin and dopamine. These compounds have been studied for their antidepressant and anxiolytic potential, as well as possible neuroprotective effects (Santos *et al*., 2020).

Phenolic compounds include acids such as chlorogenic acid, caffeic acid, and ferulic acid, known for their antioxidant, anti-inflammatory, and cardioprotective properties. These substances neutralize free radicals, contributing to cell protection and the prevention of neurodegenerative and cardiovascular diseases (Amaral, 2018).

In addition to these compounds, *P. incarnata* contains polysaccharides with immunomodulatory properties, as well as essential oils that may have relaxing and analgesic effects. The presence of cyanogenic glycosides, albeit in low concentrations, suggests a natural defense mechanism in the plant, which may influence its toxicity at high doses (Miroddi *et al*., 2013; Canella *et al*., 2019).

This method uses, an analytical technique widely used for the identification and separation of chemical compounds present in plant extracts (Dias *et al*., 2023).

Chromatography is performed using a tincture prepared in ethanol: water (65:35, v/v) with the aerial parts of the species and must be performed on a silica gel plate (Willian & Pereira, 2017). This chromatographic procedure allows the identity of the compounds present in the extract to be verified, contributing to the standardization and authenticity of the plant material analyzed. In this sense, TLC analysis is part of the set of practices that make up the quality control of plant extracts. Quality parameters, especially for products derived from the Passiflora genus, follow strict criteria established by the Brazilian Pharmacopoeia, with the aim of ensuring the safety, efficacy, and reproducibility of the final product.

The main parameters and their limits are:

Foreign Matter: The test consists of checking for the presence of materials that are not part of the plant, such as dirt, sand, or parts of other plants. The maximum limit allowed is 2.0%.

Loss on Drying: Performed using a gravimetric method, where a sample is heated to a specific temperature and the weight loss is measured. This loss represents the water and volatile content of the sample. The maximum loss limit is 11.0%.

Total Ash: The test consists of incinerating the sample at a high temperature to burn the organic matter. The resulting residue, representing the ash, is weighed. The maximum limit allowed is 10.0%.

Total Mesophilic Microorganism Count: This test determines the total number of bacteria that grow at moderate temperatures (mesophiles), verifying the microbiological suitability of the product. The sample must pass the test, i.e., it must not exceed the established limits.

Pathogenic Microorganism Survey: This test evaluates the presence of microorganisms that are harmful to health, such as and. The product must pass the test, i.e., it must be free of pathogens.

Heavy Metals: The test checks for the presence of toxic metals, such as lead, mercury, and cadmium. The sample must pass the test, not exceeding the permitted limits.

Pesticide Residues: Assesses the presence of pesticide and herbicide residues. The product must pass the test, ensuring that residue levels are below the established limits.

Foam Index: This test measures the foaming capacity of a plant extract sample after shaking. It is used as an indicator of the presence of saponins or other compounds that affect foaming.

Pharmacological Activities and Mechanism of Action

The neuropharmacological activity of *Passiflora incarnata* is associated with the combined action of the constituents present in its extracts rather than with a single isolated compound. Flavonoid C-glycosides, including vitexin, isovitexin, orientin, and isoorientin, are commonly used in the chemical characterization of the species and have been associated with its anxiolytic and sedative effects. However, differences in the plant material, extraction solvent, administered dose, and chemical standardization may influence the pharmacological response, limiting the direct attribution of the observed effects to a specific constituent (Lyca R.da Fonseca *et al.*, 2020; Janda, Wojtkowska, Jakubczyk, Antoniewicz, e Skonieczna-żydecka, 2020; Nikolova *et al.*, 2024).

The GABAergic system is considered the primary inhibitory neurotransmitter of the central nervous system. The neurotransmitter gamma-aminobutyric acid (GABA) acts on $GABA_A$ and $GABA_B$ receptors to modulate excitatory neurotransmitters such as serotonin, glutamate, norepinephrine, dopamine, and acetylcholine. The GABAergic system is the mechanism most consistently associated with the effects of *P. incarnata* on anxiety and sleep (Varinthra *et al.*, 2024) .

Experimental studies indicate that passionflower extracts may interact with $GABA_A$ and $GABA_B$ receptors and inhibit neuronal GABA uptake, thereby increasing inhibitory neurotransmission. The involvement of GABAergic pathways has also been demonstrated in experimental models investigating the anxiolytic, sedative, and antinociceptive activities of the extract. Nevertheless, the available evidence does not establish that vitexin or isovitexin alone activates chloride channels through the same mechanism as benzodiazepines. The pharmacological response should therefore be interpreted as an effect of the standardized extract and its constituent interactions (Aman *et al.*, 2016; Lyca R.da Fonseca *et al.*, 2020; Janda, Wojtkowska, Jakubczyk, Antoniewicz, e Skonieczna-żydecka, 2020; Blecharz-Klin *et al.*, 2024).

As described by (Dhawan et al., 2001) , several research groups highlight the role of the flavonoid chrysin (Zanoli U *et al.*, 2000) and maltol extracted from the plant, which are responsible for the effects on the CNS.

Evidence also suggests that *P. incarnata* may influence monoaminergic neurotransmission. In experimental studies involving rats, administration of the extract altered brain concentrations of GABA and monoamines and modified the activity or expression of enzymes involved in neurotransmitter metabolism. These findings indicate that the pharmacological effects of the species may involve broader neuromodulatory pathways beyond the GABAergic system (Jawna-Zboińska *et al.*, 2016; Blecharz-Klin *et al.*, 2024) .

It is known that alkaloids (harmanine, harmana, harmol, and harmolol) interact with the serotonin receptor (Martins de Oliveira *et al.*, 2020). Although β-carboline alkaloids, such as harmine and harmaline, can inhibit monoamine oxidase in experimental systems, their concentrations in *P. incarnata* preparations are variable and may be low. Consequently, monoamine oxidase inhibition should be presented as a possible complementary mechanism rather than as a confirmed principal pathway of the therapeutic action of the species (Jawna-Zboińska *et al.*, 2016; Blecharz-Klin *et al.*, 2024; Campos *et al.*, 2021).

In addition to its effects on the central nervous system, phenolic compounds and flavonoids present in *P. incarnata* have been associated with antioxidant and anti-inflammatory activities. In experimental models, the administration of the extract reduced lipid peroxidation, protein oxidation, inflammatory markers, and neuronal

damage. Modulation of pro- and anti-inflammatory cytokines has also been reported, suggesting that the regulation of oxidative stress and neuroinflammation may contribute to the neuroprotective and antinociceptive effects observed experimentally (Sarto *et al.*, 2018; *Gad et al.*, 2022; Amini *et al.*, 2023; Dehghani *et al.*, 2025). Nevertheless, these findings remain dependent on the extract composition and experimental model and cannot yet be extrapolated as established clinical mechanisms (Sarto *et al.*, 2018; Gad *et al.*, 2022; Amini *et al.*, 2023; Dehghani *et al.*, 2025).

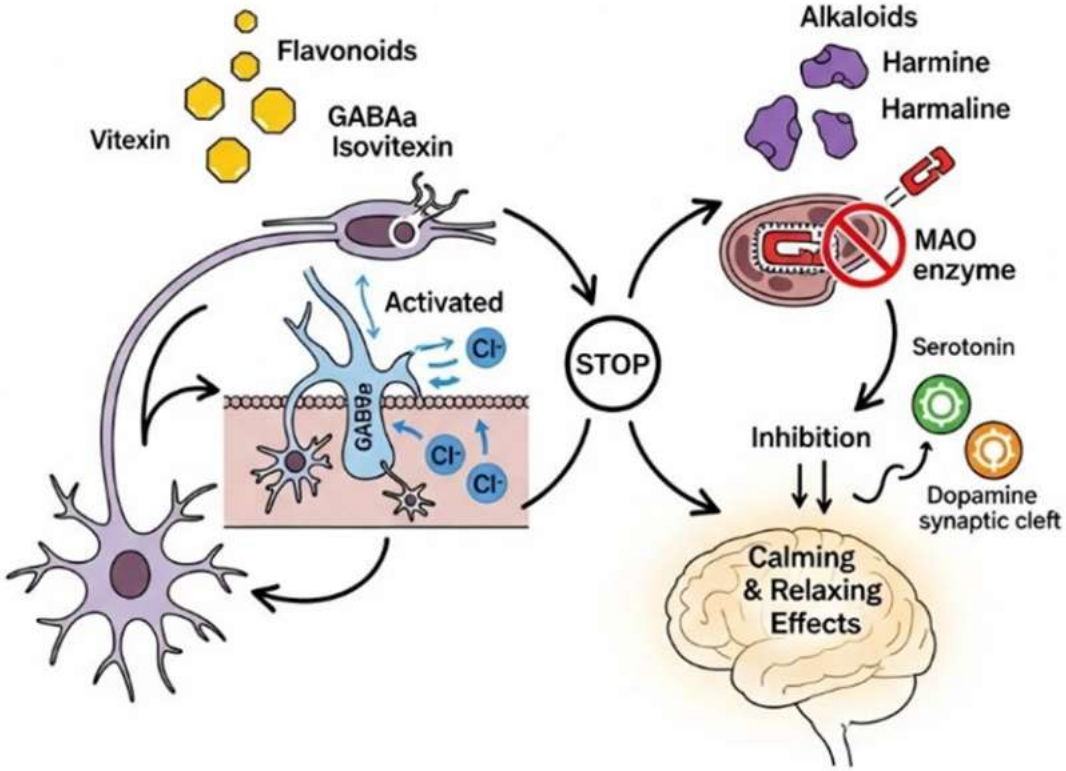


Figure 1. Mechanism of Action of Bioactive Compounds from *Passiflora incarnata* L. in the Central Nervous System. Source: Author (2025)

Overall, the available evidence indicates that *P. incarnata* presents a multi-target pharmacological profile, predominantly involving modulation of GABAergic neurotransmission (Figure 1), with possible complementary effects on monoaminergic pathways, oxidative stress, and inflammatory responses. However, the precise contribution of individual compounds and the clinical relevance of these additional mechanisms require further investigation using chemically standardized extracts and controlled clinical studies (Janda, Wojtkowska, Jakubczyk, Antoniewicz, and Skonieczna-Żydecka, 2020; Nikolova *et al.*, 2024; Campos *et al.*, 2021).

Possible Drug Interactions and Contraindications of Passiflora incarnata L.

P. incarnata, due to its calming properties, requires caution regarding possible drug interactions and contraindications. The combination of *P. incarnata* based herbal medicines with nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen, may increase the risk of bleeding by potentiating anticoagulant effects. (Sinnott-Armstrong *et al.*, 2022).

This same risk of bleeding also occurs when combined with antiplatelet drugs such as aspirin, warfarin, and heparin. In addition, when used in conjunction with benzodiazepines such as lorazepam and diazepam, or barbiturates, it can accentuate drowsiness and depression of the CNS due to the additive sedative effect (Fabiana Sari Ferreira, 2019).

Another important interaction occurs with monoamine oxidase inhibitors (MAOIs), such as isocarboxazid and phenelzine, which can intensify the adverse effects of these drugs, such as hypertensive crisis, serotonin syndrome, gastrointestinal disorders, among others. Concomitant use with stimulants, such as caffeine or guarana, also deserves attention, as it can raise blood pressure, which is particularly relevant for people with hypertension (Fabiana Sari Ferreira, 2019; Araujo *et al.*, 2021).

Regarding contraindications, the use of *Passiflora* during pregnancy and lactation is not recommended without medical supervision, due to the presence of alkaloids that can stimulate uterine contractions. Similarly, use by children under 12 years of age is not recommended without medical advice. Prolonged use of *Passiflora* can lead to dependence, as well as causing side effects such as fatigue, vomiting, and drowsiness. In rare cases, headache and insomnia may occur (Boll *et al.*, 2014).

Among the most common side effects of *Passiflora* are excessive sleepiness, nausea, vomiting, abdominal cramps, and fatigue. Less frequent effects include headache, fever, and agitation. For these reasons, it is essential that the use of *Passiflora* be monitored by a healthcare professional, thus ensuring the safety and effectiveness of its consumption (Araujo *et al.*, 2021; Kafas *et al.*, 2025; La Tempa *et al.*, 2025).

Pharmacological and Toxicological Studies

Several pharmacological studies have investigated the therapeutic applications of *P. incarnata*. In animal models, extracts reduced anxiety and improved memory performance, while also demonstrating anti-inflammatory and cardioprotective effects. In clinical contexts, trials reported reduced anxiety in dental surgery patients and improved sleep quality in individuals with mild insomnia (Dantas *et al.*, 2016; Janda, Wojtkowska, Jakubczyk, Antoniewicz, and Skonieczna-Żydecka, 2020). These findings suggest a potential role as an adjunctive therapy in anxiety and sleep disorders, although limitations such as small sample sizes and methodological heterogeneity restrict the certainty of evidence (Dantas *et al.*, 2016; Janda, Wojtkowska, Jakubczyk, Antoniewicz, and Skonieczna-Żydecka, 2020).

In metabolic studies (Sarto *et al.*, 2018) demonstrated that *P. incarnata* extract reduces cholesterol and triglycerides, preventing ventricular hypertrophy and decreasing hepatic oxidative stress, evidencing cardiovascular benefits. Its anti-inflammatory and antioxidant action was confirmed by the study, which also demonstrated its ability to reduce swelling and inflammatory markers in animal models (Hadas *et al.*, 2017).

In the context of chemical dependency, the authors (Martins de Oliveira *et al.*, 2020; Pretes *et al.*, 2023) found that *P.incarnata* can alleviate hyperalgesia associated with alcohol withdrawal, suggesting its use in the treatment of withdrawal syndrome, while the work of (Amini *et al.*, 2023) demonstrated that the extract improves autistic behaviors and reduces oxidative stress in rats, reinforcing its neuroprotective action.

In addition to experimental findings, clinical trials have corroborated the plant's therapeutic effects in humans, especially in the fields of psychiatry and sleep medicine. Clinical studies highlight its effectiveness in reducing anxiety and improving sleep quality, with fewer side effects (Dantas *et al.*, 2016) compared its effects to midazolam in dental surgeries, revealing less drowsiness and better tolerability (Azimaraghi *et al.*, 2017) indicated that *Passiflora incarnata* was more effective than oxazepam in reducing preoperative anxiety. (Pedro Carvalho Araújo *et al.*, 2025; Harit *et al.*, 2024) observed significant improvement in sleep in patients with mild insomnia (Janda, Wojtkowska, Jakubczyk, Antoniewicz, e Skonieczna-Żydecka, 2020) demonstrated its effectiveness in the treatment of generalized anxiety disorder (Mittal *et al.*, 2023).

Additional studies have shown that *Passiflora incarnata* has been used as a complement to sertraline, demonstrating therapeutic effects of the antidepressant without causing a significant increase in risks or adverse events.

Despite the evident benefits, it is essential to consider the possible risks associated with the use of *P. incarnata* extract. As highlighted in the literature (Carminati *et al.*, 2024; Jimmy de Oliveira Araújo *et al.*, 2021) , this extract may interact with sedative and anxiolytic drugs, potentiating effects such as drowsiness and CNS depression. Such interactions are particularly relevant in patients who use psychotropic drugs, as they can lead to reduced cerebral blood flow and increase the risk of adverse events. Combination with alcohol, anticoagulants (such as aspirin, warfarin, and heparin), and nonsteroidal anti-inflammatory drugs can also intensify sedative effects or increase the risk of bleeding, requiring clinical caution

Given these possibilities, the toxicity of the extract has been extensively investigated in preclinical models. Animal studies have shown that *P. incarnata* has a relatively high median lethal dose (LD50), suggesting low acute toxicity (Lyca R. da Fonseca *et al.*, 2020). They observed that intraperitoneal doses of up to 900 mg/kg in rats did not cause mortality, although doses above this value generated signs of lethargy and reduced motor activity, indicating possible CNS depressant action. Oral administration of doses up to 1,600 mg/kg did not

result in deaths, reinforcing the relative safety of the extract by this route (Santos *et al.*, 2020; Willian Lopes et al., 2017).

In subchronic and reproductive evaluations, the results also point to a satisfactory safety profile. Studies with prolonged administration of the extract in animals demonstrated the absence of systemic toxicity at therapeutic doses (Santos *et al.*, 2020). In Wistar rats exposed to the extract during pregnancy and lactation, no fetal malformations or significant adverse effects were observed, indicating the reproductive safety of the product under experimental conditions.

However, combined use with other substances may modify this safety profile. Studies combining *P. incarnata* with *Valeriana officinalis* or benzodiazepines such as lorazepam have shown an intensification of sedative effects such as muscle fatigue, dizziness, and tremors (Leite *et al.*, 2024; Deus *et al.*, 2024). This synergistic effect is attributed to the joint action on $GABA_A$ receptors, which are also modulated by synthetic anxiolytic drugs.

In humans, existing clinical trials point to safety at therapeutic doses, although mild adverse effects may occur (La Tempa *et al.*, 2025)reported that continuous use of the extract may cause nausea, drowsiness, and, in isolated cases, cardiac changes such as ventricular tachycardia. These findings reinforce the importance of rational use of the plant and the need for professional monitoring in its clinical use.

Preclinical and clinical studies highlight the therapeutic of *P. incarnata*, particularly in anxiety and sleep disorders. However, variability in extract composition, small sample sizes, and methodological differences across trials limit the certainty of evidence. Although generally well tolerated, reports of mild adverse effects such as drowsiness, nausea, and, in rare cases, cardiac alterations underscore the importance of cautious and evidence-based use (Zanardi *et al.*, 2023).

In this scenario, clinical trials represent an essential tool for confirming the efficacy and safety of the extract in humans. Studies such as those in *(Dantas et al.*, 2016; Azimaraghi *et al.*, 2017; Mittal *et al.*, 2023) support the rational and clinical use of the plant as a promising herbal alternative for anxiety and sleep disorders, with potential for integration into evidence-based medical practice.

Regulatory Landscape in Brazil (ANVISA)

The herbal medicine industry is a rapidly growing sector, driven by demand for natural and less invasive treatments for a range of health conditions. These products are formulated from plant extracts and widely used as alternatives or complements to conventional allopathic medicines. The herbal medicine market has experienced global expansion, with increased interest in natural health solutions. This is reflected in the increased production of herbal medicines to treat conditions such as anxiety, insomnia, chronic pain, digestive problems, and even hormonal disorders. Countries such as Brazil have great potential, as they have vast biodiversity and a tradition of using medicinal plants (Hasenclever *et al.*, 2017).

In this search for alternative medicines, *P.incarnata* stands out as a medicinal plant widely used in the manufacture of herbal medicines for the treatment of anxiety, acting as a nonspecific depressant of the CNS. Clinical studies conducted with patients diagnosed with anxiety and insomnia have concluded that tablets based on the dry extract of this plant are effective in controlling these conditions (Silva *et al.*, 2022).

In Brazil, the commercialization of herbal medicines derived from *Passiflora incarnata* is regulated by the National Health Surveillance Agency (ANVISA). The agency establishes strict requirements for safety, efficacy, and quality before products can be approved and registered.

According to the Brazilian Pharmacopoeia and ANVISA's resolutions, the following aspects are mandatory for herbal medicines based on *P. incarnata*:

Type of extract: primarily dry extracts or standardized fluid extracts obtained from the aerial parts of the plant.

Standardization: quantification of flavonoids (notably vitexin and isovitexin) as chemical markers. Minimum concentrations must be demonstrated by validated analytical methods such as HPLC or TLC.

Pharmaceutical forms: tablets, capsules, tinctures, oral solutions, and teas in filter bags are accepted, provided they comply with pharmacotechnical quality standards.

Quality control: includes limits for foreign matter (≤2%), loss on drying (≤11%), total ash (≤10%), microbiological safety (absence of pathogens such as *E. coli* and *Salmonella*), and heavy metals/pesticide residues below defined thresholds.

Clinical evidence: products must be supported by data from traditional safe use or clinical trials demonstrating efficacy in the treatment of anxiety, sleep disturbances, and related disorders.

Regulatory dossier: submission to ANVISA requires complete documentation of pharmacognostic characterization, stability studies, toxicological data, and clinical safety/efficacy evidence.

As shown in Table 1, all herbal medicines listed are registered or notified with ANVISA, meeting the quality, safety, and efficacy criteria required for marketing in the country. Current regulations establish specific requirements for the standardization of plant extracts used. Standardization aims to guarantee the minimum concentration of active compounds responsible for therapeutic action, thus ensuring the efficacy and predictability of clinical effects.

Table 1. Regulatory requirements for herbal medicines based on *Passiflora incarnata* L. in Brazil.

Parameter	Regulatory requirement (ANVISA)
Plant part used	Aerial parts (leaves and stems)
Extract type	Dry extract, standardized fluid extract
Standardization marker	Flavonoids (e.g., vitexin, isovitexin)
Pharmaceutical forms	Capsules, tablets, tinctures, oral solutions, teas
Quality control limits	Foreign matter ≤2%; Loss on drying ≤11%; Total ash ≤10%
Microbiological safety	Absence of *E. coli* and *Salmonella*
Toxicological requirements	Heavy metals and pesticide residues below limits
Clinical indication	Anxiety, mild insomnia, CNS disorders

Source: https://consultas.anvisa.gov.br

Application of Biotechnology

To ensure that bioactive compounds are obtained efficiently and sustainably, advanced biotechnological approaches involving in vitro cultivation, genetic engineering, and innovative methods of extraction, purification, and stabilization can be employed (Otoni *et al.*, 2024). The *in vitro* cultivation of *P. incarnata* is an innovative approach to the controlled and standardized production of its active ingredients, allowing for greater safety and efficiency in obtaining bioactive compounds. Among the techniques used, micropropagation stands out, enabling the production of genetically identical plants that are pathogen-free and have a high content of secondary metabolites (Turdiyev *et al.*, 2024).

Another strategy is the cultivation of cells and cell suspensions, which enables the large-scale production of flavonoids and alkaloids through the use of bioreactors. Additionally, it consists of applying signaling compounds, such as jasmonates and salicylic acid, capable of activating plant cell defense mechanisms. This metabolic induction promotes increased synthesis of secondary metabolites of pharmacological interest, contributing to the potentiation of the plant's therapeutic properties (Yesenia Solís-Ramos *et al.*, 2013).

Genetic engineering also emerges as a valuable resource for increasing the production of bioactive metabolites from *P. incarnata*. Gene editing using CRISPR-Cas9 technology allows the modification of key genes to intensify the synthesis of flavonoids and alkaloids, improving the plant's efficiency in producing therapeutic compounds (Li *et al.*, 2023). Another approach used is transformation via Agrobacterium tumefaciens, which consists of inserting specific genes to enhance the biosynthesis of pharmacologically active substances, promoting greater yield and standardization of plant extracts (Morillo *et al.*, 2024).

Advanced extraction methods can be used to obtain the active ingredients of *P. incarnata* efficiently and sustainably. Ultrasound-assisted extraction (UAE) uses high-frequency sound waves to cause cavitation, breaking down plant cells and effectively releasing bioactive compounds (Prado *et al.*, 2025).

Microwave-Assisted Extraction (MAE) uses electromagnetic waves to selectively heat molecules, optimizing the extraction yield of the desired compounds (Batista *et al.*, 2025). Another innovative method is Supercritical CO_2 Extraction (SFE), which uses carbon dioxide in a supercritical state as an environmentally friendly solvent, allowing high-purity extracts to be obtained without the presence of toxic residues, making the process safer and more environmentally sustainable (Marìn-Tello *et al.*, 2024; Meneses *et al.*, 2024).

After extraction, bioactive compounds must undergo purification and stabilization processes to ensure their efficacy and prolong their pharmaceutical viability. High-performance liquid chromatography (HPLC) is widely used to separate and quantify active compounds, ensuring a high standard of quality in the final products (Marìn-Tello *et al.*, 2024).

Nanoencapsulation is a relevant technique and an efficacy strategy in advanced drug delivery systems, offering robust protection of bioactive compounds against physicochemical degradation. This encapsulation significantly enhances both bioavailability and therapeutic performance. Complementarily, lyophilization is an

advanced dehidratation technique by sublimation and employed to stabilize phytochemical constituents within plant extracts, thereby extending shelf life and preserving the integrity of their bioactive properties over prolonged storage periods. (Deepika *et al*., 2024).

However, for this process to be viable and ethically responsible, it is essential that the exploitation of *P. incarnata* occurs in a sustainable manner, considering both economic and environmental aspects. The economic viability of the plant is associated with its commercial production through controlled cultivation, ensuring a stable and standardized supply for the pharmaceutical and herbal medicine industries. Similarly, biodiversity conservation is essential to prevent excessive harvesting in the wild, and it is crucial to encourage sustainable agricultural practices that ensure the preservation of ecosystems (Cueva-Yesquén *et al*., 2024).

Proper crop management should include agroecological techniques, such as the efficient use of natural resources, biological pest control, and reduction of environmental impact, ensuring the maintenance of soil quality and long-term productivity. These strategies contribute to the sustainability of *P. incarnata*, promoting economic and environmental benefits simultaneously (Sangoquiza-Caiza *et al*., 2023).

Discussion

The findings of this integrative review suggest that *P. incarnata* contains flavonoids and β-carboline alkaloids associated with anxiolytic and sedative properties (Pretes *et al*., 2023). While preclinical and clinical studies indicate benefits for anxiety and sleep disorders, limitations such as small sample sizes and heterogeneity reduce the certainty of evidence. These limitations highlight the need for further large-scale, randomized controlled trials to establish efficacy and long-term safety (Amaral, 2018; Liu *et al*., 2017).

Clinical and preclinical studies have indicated that *P. incarnata* has anxiolytic, sedative, anti-inflammatory, antioxidant, and neuroprotective effects. In animal models, administration of the extract resulted in reduced anxiety and improved memory, in addition to presenting anti-inflammatory and cardioprotective effects (Santos *et al*., 2020; Zanardi *et al*., 2023). Clinical trials with humans have shown a reduction in anxiety in surgical contexts and improved sleep quality, comparable to conventional drugs but with fewer adverse effects (Dias *et al*., 2023) .

The quality control of *P. incarnata* extract followed strict criteria, including analyses of foreign matter, loss on drying, total ash, microbiological contamination, heavy metals, and pesticide residues, ensuring its safety for pharmaceutical use (Lyca R. da Fonseca *et al*., 2020; Santos *et al*., 2020).

The findings reinforce the therapeutic potential of *P. incarnata*, in line with its traditional use in folk medicine Bortoluzzi *et al*., 2020; Miroddi *et al*., 2013). These effects are consistent with modulation of neurotransmitter systems, although further studies are needed to clarify pathways and long-term safety (Garcia *et al*., 2024).

Clinical studies suggest benefits of *P. incarnata* in managing anxiety and insomnia, indicating its promise as an alternative or adjunct to conventional drugs. Nonetheless, possible adverse effects and drug–drug interactions, particularly with anticoagulants, benzodiazepines, or barbiturates, warrant cautious use and further investigation (Otoni *et al*., 2024).

The use of plant bioactives combined with investment in technological innovations has led to significant advances for the pharmaceutical industry and, consequently, for health. Biotechnology has emerged as a field of knowledge that develops efficient pharmacological strategies, contributing to the sustainable exploitation of botanical resources, adding economic value to native ecosystems, and contributing to innovations with applications in the field of health.(Ahmad *et a*l., 2025; Chelliah *et al*., 2025; Dincheva *et al*., 2025).

Methods such as nanoencapsulation and lyophilization can optimize the bioavailability and stability of active compounds, expanding their application in the pharmaceutical industry (AzizoÓlu *et al*., 2024; Larit *et al*., 2023)

Conclusion

Despite the favorable safety profile of *Passiflora incarnata* L., further studies are needed to explore its potential in neurological and inflammatory treatments, as well as to validate its large-scale application in the pharmaceutical industry. Furthermore, it is necessary to implement sustainable measures aimed at preserving the species' availability and minimizing environmental impacts.

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