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Review

A Systematic Review of Neurobiological Mechanisms of *Passiflora*: Beyond GABA Modulation

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Abstract

Background/Objectives: *Passiflora* (passionflower), traditionally used for anxiety and insomnia, is primarily known for GABAergic modulation. However, evidence suggests broader neuropharmacological actions. This review aimed to systematically explore non-GABAergic mechanisms of *Passiflora*. **Methods**: We performed a systematic review following PRISMA Guidelines (PROSPERO: CRD420251028681). PubMed/Medline, PsycINFO, Embase, Web of Science, and Scopus were searched for original research on non-GABA neurobiological mechanisms of *Passiflora* species (*P. incarnata*, *P. edulis*, *P. caerulea*, *P. actinia*, *P. foetida*). Studies were screened and assessed for eligibility, and data on design, *Passiflora* preparation, mechanisms, and main findings were extracted. **Results**: Thirteen studies revealed diverse non-GABAergic actions. *Passiflora* modulates opioidergic and nicotinic cholinergic systems (relevant to analgesia), monoaminergic pathways (affecting dopamine, norepinephrine, serotonin), and the glutamatergic system (offering neuroprotection via NMDA receptor inhibition). It also exhibits significant anti-inflammatory and antioxidant effects (reducing cytokines, activating Nrf2) and modulates the HPA axis (reducing stress hormones). Other mechanisms include gut microbiota modulation and metabolic effects. **Conclusions**: *Passiflora*'s therapeutic potential extends beyond GABA, involving multiple neurotransmitter systems and neuroprotective, anti-inflammatory, antioxidant, and HPA axis-regulating activities. This multi-target profile likely contributes to its clinical efficacy in conditions like anxiety, pain, and stress, potentially with a favorable side-effect profile. Further research, including mechanistic studies and clinical trials with relevant biomarkers, is needed to fully elucidate its complex pharmacology.

Keywords: *Passiflora*; neurobiological mechanisms; GABA modulation; flavonoids; opioidergic system; monoaminergic system; glutamatergic system; neuroprotection; HPA axis; anti-inflammatory

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1. Introduction

Passiflora, commonly known as passionflower, encompasses a diverse genus of plants with a long history in traditional medicine across multiple cultures. These plants have been employed for centuries to address conditions such as anxiety, insomnia, and stress-related disorders [1]. Although *Passiflora* contains over 500 species, scientific research has predominantly focused on species like *Passiflora incarnata*, *P. edulis*, *P. caerulea*, and *P. actinia* [1,2]. These species demonstrate complex phytochemical profiles containing medicinally relevant flavonoids, including chrysin, apigenin, vitexin, and isovitexin, along with indole-derived β-carboline alkaloids like harmine and harmaline [1,3,4]. Researchers have prepared *Passiflora* extracts from different plant components, including aerial portions, leaves, fruits, and seeds, through various extraction techniques, such as hydroalcoholic and methanolic methods. These extracts have consistently demonstrated a range of neurological effects in both preclinical models and human clinical trials [5,6].

Historically, the scientific investigation of *Passiflora*'s well-documented anxiolytic effects has focused primarily on its interaction with the γ-aminobutyric acid (GABA) system, the central nervous system's major inhibitory neurotransmitter network [7]. Flavonoid components, particularly chrysin and apigenin, have been shown to selectively bind to the benzodiazepine (BZ) site on GABA receptors [8,9]. This interaction typically manifests as partial agonism, enhancing GABAergic inhibition and thereby reducing neuronal hyperexcitability. Unlike full receptor activation, this mechanism produces calming effects while generally avoiding the significant sedation [10], muscle relaxation, or cognitive impairment characteristic of conventional benzodiazepines [3,11,12]. Furthermore, evidence suggests that *Passiflora* extracts may also inhibit the synaptic reuptake of GABA, prolonging its inhibitory action [7]. For many years, this modulation of the GABAergic pathway has been considered the primary explanation for *Passiflora*'s therapeutic benefits in anxiety and related conditions.

However, attributing *Passiflora*'s broad-spectrum neurological effects exclusively to GABA modulation likely represents an incomplete understanding. Growing evidence suggests that the plant engages multiple distinct neurobiological pathways, which collectively contribute significantly to its diverse effects, ranging from analgesia and antidepressant activity to neuroprotection and stress adaptation [1]. While these additional mechanisms remain less studied than GABAergic interactions, they are emerging as critical components of *Passiflora*'s overall pharmacological profile and represent a promising yet underexplored area of research. Emerging research suggests involvement of the opioidergic system in *Passiflora*'s analgesic properties, which is particularly demonstrated in preclinical models by the reversal of its neuropathic pain relief following administration of the opioid antagonist naloxone [5,13]. Intriguingly, the identification of oleamide, a fatty acid amide with CB1 receptor affinity, suggests a potential contribution of cannabimimetic pathways to *Passiflora*'s analgesic and sedative actions [5]. Furthermore, *Passiflora* exhibits multi-target activity within monoaminergic systems, with studies reporting altered levels of dopamine and norepinephrine in specific brain regions [14], while its antidepressant-like effects correlate with serotonergic modulation, likely mediated by the *β-carboline* alkaloid inhibition of monoamine oxidase A (MAO-A) [4,15].

Compelling evidence further highlights neuroprotective effects via glutamatergic modulation, where compounds like isovitexin and vitexin mitigate glutamate-induced excitotoxicity through NMDA receptor inhibition [16,17]. Anti-inflammatory [18] and antioxidant pathways are also implicated, with *Passiflora* extracts shown to reduce pro-inflammatory markers like TNF-α and IL-1β, potentially by suppressing NF-κB and MAPK signaling, while activating Nrf2-mediated antioxidant defenses [19,20]. *Passiflora* also regulates the hypothalamic–pituitary–adrenal (HPA) axis activity, pointing to direct effects

on stress physiology by lowering corticosterone in stressed animals [12] and improving stress and sleep outcomes in humans [6]. Other potential contributing mechanisms include nicotinic cholinergic analgesia [13] and even gut microbiota beneficial modulation, which may indirectly influence brain function [19]. This review aims to systematically explore *Passiflora*'s complex and multi-target neuropharmacology, which extends far beyond the classical GABAergic framework, providing a more comprehensive understanding of its actions and implications.

2. Materials and Methods

A systematic literature search was performed (PROSPERO: CRD420251028681) to identify original research investigating the neurobiological mechanisms of *Passiflora* species, focusing specifically on pathways beyond GABAergic modulation (Table S1). The search aimed to capture a comprehensive view of the plant's diverse neurological effects.

The initial identification phase involved searching the following five electronic databases: PubMed/Medline (yielding 696 records), PsycINFO (24 records), Embase (1167 records), Web of Science (1503 records), and Scopus (2309 records), along with other registers. This search resulted in a total of 5699 records. Search terms included "*Passiflora incarnata*", "passionflower", and "neurobiological mechanism", combined with specific pathway-related keywords like "opioidergic", "glutamatergic", "monoaminergic", "HPA axis", "neuroinflammatory", and "cannabinoid". Following the initial retrieval, 853 duplicate records were identified and removed.

The remaining 4846 unique records underwent title and abstract screening. The primary criterion for inclusion at this stage was the investigation of any neurobiological mechanism of *Passiflora* species other than GABA modulation. This screening led to the exclusion of 4824 records that did not meet the focus of the review. Full-text articles were then sought for the 22 potentially relevant reports. All 22 reports were retrieved and assessed for final eligibility (Table S2).

Eligibility criteria required studies to be original research (including preclinical models, human trials, phytochemical analyses with mechanistic data, or neurobiological assays) reporting specific non-GABA neurobiological mechanisms, pharmacological pathways, or receptor interactions. Studies were excluded from this review if they met several criteria related to scope, methodology, and reporting. Exclusions encompassed research focusing solely on GABAergic activity or only on peripheral mechanisms without a clear link to central neurobiology, as well as studies reporting only clinical outcomes without mechanistic data. Non-original research such as reviews, abstracts, and case reports were excluded, along with studies lacking sufficient methodological quality. Furthermore, studies were ineligible if they used multi-herb preparations where *Passiflora*'s effects could not be isolated, if they failed to clearly identify the *Passiflora* species or detail the extraction method, if they employed in vitro models not relevant to neurobiology (e.g., non-neuronal cells), or if they reported mechanistic findings without adequate quantifiable data or methodological detail. The appropriate tools used to assess the quality and risk of bias for each included study, based on study design, were RoB 2 (Risk of Bias 2 tool), the SYRCLE Risk of Bias tool (Systematic Review Centre for Laboratory animal Experimentation), and an adapted JBI checklist for analytical studies (Joanna Briggs Institute). Detailed results of the assessments using these specific tools are available in the Supplementary Material (Table S3). The study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Table S4) [21].

3. Results

After going through the study selection process, we detail the characteristics of the included studies, encompassing their design, the *Passiflora* species and preparations investigated, and the specific non-GABA neurobiological pathways examined. Finally, we synthesize the key findings from these studies regarding the diverse mechanisms engaged by *Passiflora* beyond GABAergic modulation.

3.1. Study Selection

Nine reports were excluded for the following reasons: three focused exclusively on GABAergic mechanisms rather than other neurobiological pathways (Reason 1), four were systematic or narrative reviews (Reason 2), and two used multi-herb preparations without differentiating *Passiflora*'s specific effects from other botanicals (Reason 3). A final set of 13 studies met all inclusion criteria, and these studies were included in this systematic review (Figure 1). These studies encompassed various experimental designs evaluating non-GABAergic neurobiological effects of *Passiflora* extracts or isolated compounds. Key data were extracted from each included study, covering aspects such as study design, experimental model, *Passiflora* species and preparation details, identified bioactive compounds, specific non-GABA mechanisms investigated, molecular targets, signaling pathways, and principal findings.

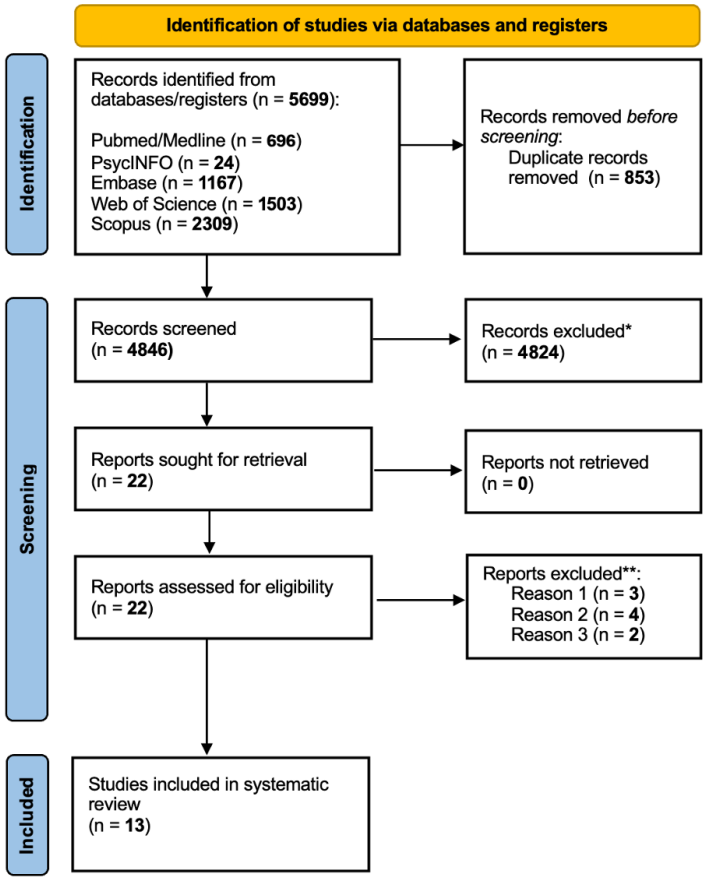


Figure 1. PRISMA flow diagram. (*) Records excluded during the screening phase were removed based on title and abstract review if they did not meet the various criteria related to the review's focus (primarily, not investigating non-GABA mechanisms). (**) Reports that excluded following full-text assessment were removed specifically for Reason 1 (focused exclusively on GABAergic mechanisms; $n = 3$), Reason 2 (systematic or narrative reviews; $n = 4$), or Reason 3 (used multi-herb preparations where *Passiflora*'s effects were indistinguishable; $n = 2$).

3.2. Study Characteristics and Main Features

This review encompasses a range of studies investigating the neurobiological effects of various *Passiflora* species beyond the well-documented GABAergic system. The included research utilizes diverse methodologies, including in vivo animal models (rats, mice) subjected to stress, nociceptive, behavioral, or disease-induction protocols, as well as in vitro assays employing neuronal cultures, macrophages, gut simulators, and ex vivo tissue preparations. Clinical evidence from human randomized controlled trials and systematic reviews further contribute to the dataset. Species investigated include *Passiflora incarnata*, *P. caerulea*, *P. actinia*, *P. foetida*, *P. edulis*, and *P. subpeltata*, with preparations ranging from crude hydroalcoholic or methanolic extracts and aqueous infusions to purified fractions, specific flavonoid compounds like isovitexin and vitexin, and standardized commercial extracts. The investigated non-GABA neurobiological foci span multiple systems, including opioidergic, cannabinoid, monoaminergic, glutamatergic, cholinergic, neuroinflammatory, HPA axis, antioxidant, metabolic, and cardiovascular pathways (Figure 2 and Table 1).

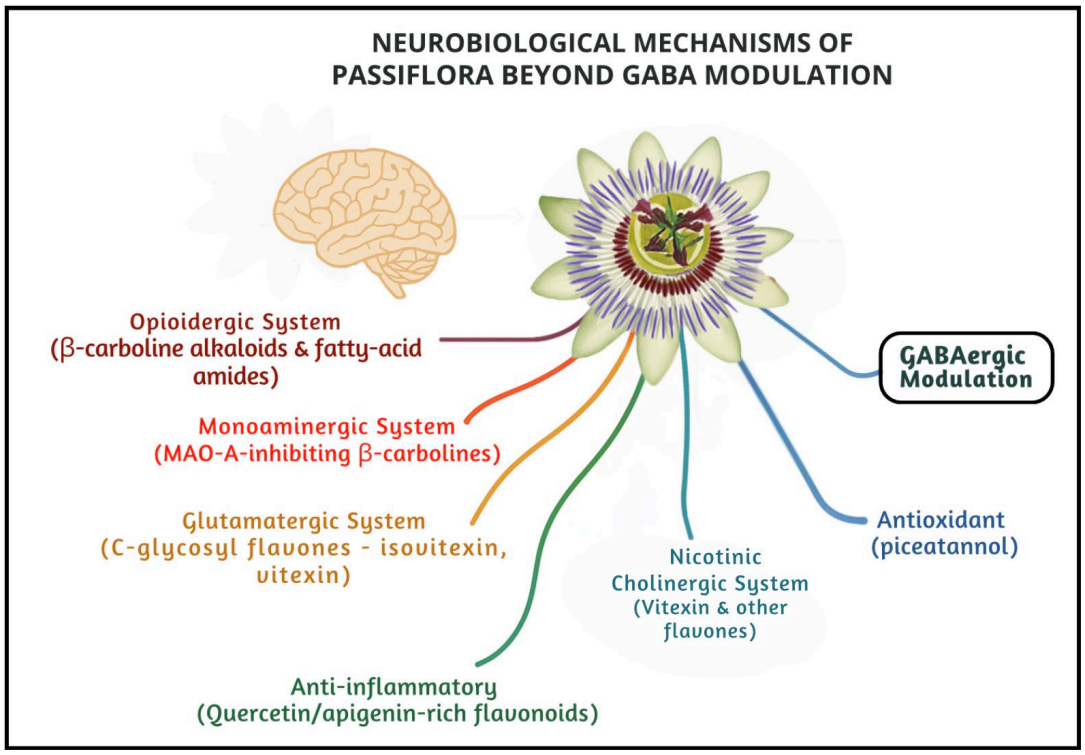


Figure 2. Multi-target neuropharmacology of *Passiflora* extracts. The figure illustrates mechanisms extending beyond GABAergic (γ-aminobutyric acid) modulation, including opioidergic, monoaminergic (dopamine [DA], serotonin [5-HT], and norepinephrine [NE] pathways for mood regulation), glutamatergic, and cholinergic (nicotinic) systems, with additional anti-inflammatory and antioxidant effects.

Two studies provide evidence for the involvement of opioidergic and related systems [5,13]. Analgesic effects of *P. incarnata* extracts were reported to be reversed by the opioid antagonist naloxone in mouse models of nociception, and the modulation of opioid withdrawal symptoms was observed [5,13]. Additionally, a potential role for the cannabinoid system was suggested based on the presence of oleamide in *P. incarnata* extracts, although direct antagonist studies were lacking [5]. A nicotinic cholinergic mechanism, distinct from muscarinic pathways, was also implicated in the analgesic effects of a *P. incarnata* fraction, as demonstrated by reversal with mecamylamine [13].

Table 1. Characteristics of included studies.

Study (Author, Year)	Study Design and Model	*Passiflora* Species and Preparation	Focus of Non-GABA Investigation
Aman et al., 2016 [5]	In vivo; mice (acute nociception/behavior), rats (diabetic neuropathy—STZ induced)	*Passiflora incarnata* L.; methanolic extract (PI-ME) from aerial parts	Opioidergic system (naloxone reversal), cannabinoid system (speculative via oleamide)
Feliú-Hemmelmann et al., 2013 [12]	In vivo; male CF-1 mice (chronic stress—movement restriction)	*Passiflora caerulea*; aqueous infusion (MELIPASS®—combined w/Melissa officinalis)	HPA axis modulation (corticosterone), metabolic effects (glucose), immune modulation (spleen)
Blecharz-Klin et al., 2024 [14]	In vivo; male Wistar rats (chronic admin, behavioral tests)	*Passiflora incarnata* L.; standardized dry extract (aerial parts)	Monoaminergic system (5-HT, DA, NA levels/metabolites in CNS), glutamatergic system (GLU, ASP levels)
dos Santos et al., 2016 [16]	Combined in vivo/ex vivo/in vitro; mice, mouse hippocampal slices (glutamate challenge)	*Passiflora actinia* (primary), *P. incarnata*; hydroalcoholic extract (leaves), isovitexin	Glutamatergic system modulation (neuroprotection vs. excitotoxicity), antioxidant (speculative via isovitexin), hormesis (speculative)
Han et al., 2023 [19]	In vitro; RAW264.7 macrophages (LPS), human gut microbiota simulator (BFBL model)	*Passiflora foetida*; flavonoid-rich fraction (PFF) from fruit	Neuroinflammatory modulation (cytokines, MAPK, PI3K/Akt, NF-κB pathways), gut microbiota modulation (bacterial shifts, SCFA production)
Harit et al., 2024 [6]	Clinical trial (RCT); human adults with stress/sleep problems	*Passiflora incarnata*; standardized extract (capsule)	HPA axis modulation (stress perception, cortisol trend), sleep architecture regulation, cognitive function enhancement (concentration, memory)
Ingale and Kasture, 2012 [13]	In vivo; Swiss albino mice (analgesic tests—formalin, eye-wiping)	*Passiflora incarnata*; n-butanol fraction (BEPI) and sub-fraction (BEPI-F1) from leaf ethanolic extract	Opioidergic system (naloxone reversal), nicotinic cholinergic mechanism (mecamylamine reversal)
Jafarpoor et al., 2014 [4]	In vivo; mice (forced swim test—antidepressant model)	*Passiflora incarnata*; extract	Monoaminergic system, GABA inverse agonism
Yang et al., 2014 [17]	In vitro; mouse cortical neurons (NMDA excitotoxicity)	Studied vitexin (flavonoid found in *Passiflora*)	Glutamatergic system (NMDA/NR2B inhibition, $\downarrow Ca^{2+}$ influx), apoptotic pathways

Table 1. *Cont.*

Study (Author, Year)	Study Design and Model	*Passiflora* Species and Preparation	Focus of Non-GABA Investigation
Saravanan et al., 2014 [22]	Combined in vitro (antioxidant assays: DPPH, ABTS, metal chelating, superoxide radical scavenging) and in vivo (analgesic, anti-inflammatory, antipyretic in mice and rats) study	*Passiflora subpeltata* (leaves); successive Soxhlet extraction (petroleum ether, chloroform, acetone, methanol); acetone extract used for in vivo tests	Antioxidant pathways, anti-inflammatory mechanisms, prostaglandin inhibition, peripheral and central pain modulation
Viera et al., 2022 [23]	In vitro chemical analysis	*P. edulis f. flavicarpa*, *P. edulis f. edulis*, *P. alata*, *Passiflora* sp.; methanol/water/formic acid extraction of lyophilized pulp	Antioxidant mechanisms (ABTS, FRAP); potential neuroprotective effects via polyphenols, flavonoids, carotenoids, vitamin C
Sukketsiri et al., 2023 [20]	In vitro (antioxidant, anti-lipid, anti-inflammatory); ex vivo (rat aorta vasodilation)	*Passiflora edulis*; seed ethanolic extract (PSEE), fruit/pulp water extract (PFWE)	Antioxidant, anti-lipid (enzyme inhibition), anti-inflammatory (NO reduction), vasodilation
Alves et al., 2020 [15]	In vivo; mice (forced swimming test, open-field test)	*Passiflora edulis f. flavicarpa*; flavonoid-rich extract from leaves (5.21 mg/g isoorientin), purified isoorientin	Monoaminergic system (antidepressant-like effects of isoorientin); potency comparable to nortriptyline; no locomotor effects

Note: *P.* denotes the genus *Passiflora* and sp. refers to a single species. Abbreviations for neurotransmitters and related molecules include 5-HT (serotonin), DA (dopamine), NA (noradrenaline/norepinephrine), GLU (glutamate), and ASP (aspartate), often measured in the CNS (central nervous system). Key pathways and systems mentioned are HPA axis (hypothalamic–pituitary–adrenal axis), NMDA (N-methyl-D-aspartate) receptors (including the NR2B subunit), MAPK (mitogen-activated protein kinase), PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Experimental terms include STZ (streptozotocin, for inducing diabetes), LPS (lipopolysaccharide), BFBL (Bionic Fisogastrointestinal BioLogic gut simulator), SCFA (short-chain fatty acid), Ca^{2+} (calcium ion), NO (nitric oxide), RCT (randomized controlled trial), and antioxidant assays DPPH, ABTS, and FRAP. Specific extract abbreviations like PI-ME (*P. incarnata* methanolic extract), BEPI (n-butanol extract of *P. incarnata*), PSEE (*P. edulis* seed ethanolic extract), and PFWE (*P. edulis* fruit/pulp water extract) refer to preparations used in the respective studies; MELIPASS® is a specific product combining *P. caerulea* with Melissa officinalis.

The modulation of monoaminergic neurotransmission represents another significant non-GABA mechanism. Chronic administration of *P. incarnata* extract altered dopamine, norepinephrine, and serotonin metabolite levels in specific rat brain regions, notably increasing spinal dopamine [14]. Furthermore, *P. incarnata* exhibited behavioral effects in mice consistent with serotonergic antidepressants, potentially mediated by MAO-A inhibition attributed to beta-carboline alkaloids like harmine, which may also interact directly with 5-HT2A receptors [4].

Interactions with the glutamatergic system were investigated, revealing neuroprotective effects. *Passiflora actinia* hydroalcoholic extract and its constituent isovitexin protected mouse hippocampal slices against glutamate-induced excitotoxicity [16]. Mechanistic studies focusing on vitexin, a flavonoid present in *Passiflora*, demonstrated inhibition of NMDA-induced neurotoxicity in primary cortical neurons, linked specifically to downregulation of the NR2B subunit and subsequent reduction in calcium influx [17]. Blecharz-Klin et al. (2024) [14] also reported altered levels of glutamate and aspartate in rat CNS tissues following *P. incarnata* administration.

Evidence points towards modulation of the stress response and neuroinflammation. *Passiflora caerulea* infusion (in combination with *Melissa officinalis*) reduced plasma corticosterone levels in chronically stressed mice [12], while a clinical trial using *P. incarnata* reported significant reductions in perceived stress scores in humans [6]. Similarly, a flavonoid-rich fraction from *P. foetida* suppressed pro-inflammatory mediators (NO, TNF-α, IL-6) and associated signaling pathways (MAPK, PI3K/Akt) in LPS-stimulated macrophages. Related antioxidant mechanisms were also noted, including modulation of GGT and potential contributions from isovitexin [16], alongside broader antioxidant activities reported for *P. edulis* extracts involving the Keap1-Nrf2 pathway and direct ROS scavenging [20].

Furthermore, *Passiflora subpeltata* leaf acetone extract demonstrated antioxidant effects in vitro (DPPH, ABTS, metal chelating, superoxide radical scavenging assays) and in vivo (mice and rats), alongside anti-inflammatory and antipyretic activities, suggesting potential involvement in antioxidant pathways, anti-inflammatory mechanisms, prostaglandin inhibition, and peripheral and central pain modulation [22]. In vitro chemical analysis of *P. edulis f. flavicarpa*, *P. edulis f. edulis*, *P. alata*, and *Passiflora* sp. pulp extracts also revealed antioxidant mechanisms (ABTS, FRAP) and potential neuroprotective effects attributed to polyphenols, flavonoids, carotenoids, and vitamin C [23].

Expanding on the antidepressant potential, a study by Alves et al. (2020) [15] investigated the antidepressant effects of isoorientin, a flavonoid isolated from *Passiflora edulis f. flavicarpa* (yellow passion fruit) leaves. The researchers optimized extraction methods to obtain a flavonoid-rich extract (FRE) with a high isoorientin content (5.21 mg/g). Both the FRE (50–100 mg/kg, p.o.) and purified isoorientin (10 mg/kg, p.o.) exhibited significant antidepressant-like effects in mice using the forced swimming test, comparable to the conventional antidepressant nortriptyline. Specifically, isoorientin (10 mg/kg) reduced immobility time by 75.4% and the FRE (100 mg/kg) by 49.2%. Importantly, neither the extract nor isoorientin affected locomotor activity in the open-field test, indicating that the antidepressant effect was not due to general motor stimulation. This study provides compelling evidence that isoorientin is likely a key component responsible for the antidepressant effects of *P. edulis* leaves, suggesting its potential for the development of novel herbal treatments for depression and representing a 10-fold increase in antidepressant potency compared to previous crude extracts of the plant [15].

Additional non-GABA biological activities were reported across different species and preparations. *Passiflora foetida* flavonoids modulated gut microbiota composition and increased short-chain fatty acid production in an in vitro simulator [19]. Extracts from *P. edulis* demonstrated anti-lipid activities via the inhibition of pancreatic lipase and

cholesterol esterase, as well as ex vivo vasodilation effects [20]. The clinical trial with *P. incarnata* also documented improvements in sleep architecture parameters and cognitive functions like concentration and memory [6]. Preliminary metabolic and immune effects were also observed with *P. caerulea* administration in mice [12].

3.3. Preclinical in Vivo Studies Investigating Non-GABA Neurobiological Mechanisms of *Passiflora incarnata*

Preclinical in vivo investigations using rodent models revealed that *Passiflora incarnata* engages multiple neurobiological mechanisms beyond GABAergic modulation [4,5,13,14,22]. The reviewed studies employed various extracts (e.g., hydroalcoholic, methanolic, standardized dry, n-butanol fraction, acetone leaf) administered through different routes (oral gavage, intraperitoneal injection, in drinking water) over acute or chronic periods (single dose up to 47 days). These studies investigated opioidergic, cholinergic, monoaminergic, inflammatory, and antioxidant stress pathways in rats (Wistar, Sprague Dawley) and mice (Swiss albino, BALB/c, other strains unspecified) under conditions including pain models (formalin test, eye-wiping test, acetic acid-induced writhing, diabetic neuropathy), inflammation models (paw edema), fever models (yeast-induced), stress paradigms (immobilization), depression models (Forced Swim Test), and evaluations of baseline neurotransmitter levels. The key findings regarding these non-GABAergic mechanisms derived from these preclinical models, including treatment details, are systematically presented in Table 2.

Administration of the opioid antagonist naloxone partially reversed the antinociceptive effects of both a methanolic extract (Pl-ME) in mouse acute pain/anxiety and rat diabetic neuropathy models [5] and an n-butanol fraction (BEPI) following intraperitoneal injection in mouse acute pain tests (formalin, eye-wiping) [13]. The study by Ingale and Kasture (2012) [13] further indicated the contribution of the nicotinic cholinergic system, as the analgesic effect of the BEPI fraction was significantly blocked by the nicotinic antagonist mecamylamine in both assays in Swiss albino mice.

Modulation of central monoaminergic neurotransmitter systems has also been observed. Chronic administration (47 days) of a standardized *P. incarnata* dry extract via drinking water resulted in significant alterations in regional neurotransmitter levels in male Wistar rats, specifically increasing dopamine concentrations in the spinal cord while decreasing norepinephrine levels in the cerebellum, alongside modest changes in serotonin metabolism (e.g., increased spinal 5-HIAA) measured by high-performance liquid chromatography (HPLC) [14]. In a separate study using the forced swim test (a depression model) in mice, acute administration of a *P. incarnata* extract induced an increase in swimming time, a behavioral profile similar to SSRIs and consistent with serotonergic activity; potential MAO-A inhibition was also inferred based on the known presence of beta-carboline alkaloids [4].

In a rat model of immobilization stress, pre-treatment with a hydroalcoholic *P. incarnata* extract significantly attenuated stress-induced increases in serum levels of the inflammatory markers TNF-α and IL-1 and the oxidative stress marker MDA [5]. Further supporting these mechanisms, Saravanan et al. (2014) [22] showed that an acetone leaf extract of *P. incarnata* administered orally exerted dose-dependent analgesic, anti-inflammatory (reducing paw edema, inhibiting mediators like prostaglandins, histamine, bradykinin), and antipyretic effects in mice and rats across various models. The study also highlighted the extract's antioxidant potential (DPPH IC_{50} = 27.9 μg/mL) and identified antioxidant phenolics like quercetin, apigenin, and catechin. Additionally, the identification via GC-MS of high levels of oleamide, a known CB1 receptor modulator, in the methanolic extract used by Aman et al. (2016) [5], led to the suggestion of potential, though experimentally unconfirmed in that study, involvement of the cannabinoid system in the plant's pharmacological profile.

Table 2. Preclinical in vivo studies investigating non-GABA neurobiological mechanisms of *Passiflora incarnata*.

Study (Author, Year)	Non-GABA Mechanism Targeted	Key Finding Summary	Finding Details/Method	Animal Model	Treatment Details
Aman et al. (2016) [5]	Opioidergic system; cannabinoid system (potential)	Partial opioid role in analgesia; potential CB1 involvement	High oleamide (known CB1 modulator) identified via GC-MS (CB role inferred).	BALB/c mice (acute pain/anxiety); Sprague Dawley rats (diabetic neuropathy).	Methanolic extract (PI-ME); mice: 100–600 mg/kg p.o.; rats: 200–300 mg/kg p.o.; acute and chronic treatment.
Blecharz-Klin et al. (2024) [14]	Monoaminergic system (DA, NE, 5-HT)	Altered DA and NE levels in specific CNS regions	↑ Spinal cord DA; ↓ cerebellar NE; modest changes in 5-HIAA metabolism (e.g., ↑ spinal). Measured via HPLC.	Male Wistar rats; chronic administration model.	Standardized dry extract; 30, 100, 300 mg/kg/day p.o. (in drinking water); 47 days.
Ingale and Kasture (2012) [13]	Opioidergic system; nicotinic cholinergic system	Opioid and nicotinic receptors involved in analgesia	Naloxone and mecamylamine reversed analgesic effect of n-butanol fraction (BEPI) in formalin and eye-wipe tests.	Swiss albino mice; formalin test and eye-wiping test (acute pain models).	n-Butanol fraction (BEPI) and sub-fraction (BEPI-F1); BEPI: 150, 300 mg/kg i.p.; BEPI-F1: 300 mg/kg i.p.; single dose.
Saravanan et al. (2014) [22]	Antioxidant system; anti-inflammatory mediators (e.g., prostaglandins, histamine, bradykinin)	Dose-dependent analgesic, anti-inflammatory, antipyretic effects via non-GABA pathways	↓ Writhing and paw edema; ↓ yeast-induced fever; biphasic effects in formalin test; IC_{50} for DPPH = 27.9 µg/mL; high phenolic/tannin content measured; HPLC identified quercetin, apigenin, catechin.	Mice and rats (acetic acid-induced writhing, formalin, paw edema, yeast-induced fever models).	Acetone leaf extract; 200 and 400 mg/kg p.o.
Jafarpoor et al. (2014) [4]	Monoaminergic system (serotonergic; MAO-A inferred)	Serotonergic-like antidepressant effect	↑ Swimming time in forced swim test (FST), similar to SSRIs; beta-carbolines present suggest MAO-A inhibition (inferred).	Mice (species/strain not specified); FST (depression model).	*P. incarnata* extract (type not specified); 200, 400, 800 mg/kg (route likely p.o. or i.p.); acute treatment.

Note: Dosing is expressed in mg/kg (milligrams of substance per kilogram of body weight), administered either p.o. (per os, meaning orally) or i.p. (intraperitoneally). Specific preparations include PI-ME (*Passiflora incarnata* methanolic extract), BEPI (n-butanol extract of *P. incarnata*), and its sub-fraction BEPI-F1. Neurotransmitters mentioned are DA (dopamine), NE (norepinephrine), and 5-HT (serotonin), along with the serotonin metabolite 5-HIAA (5-hydroxyindoleacetic acid), often measured in the CNS (central nervous system). Analytical methods include GC-MS (gas chromatography-mass spectrometry) and HPLC (high-performance liquid chromatography). Receptors like CB1 (cannabinoid receptor type 1) and enzymes such as MAO-A (monoamine oxidase A) are discussed. The FST (forced swim test) is a behavioral model, and the DPPH assay measures antioxidant capacity, with potency indicated by IC_{50} (half maximal inhibitory concentration) in µg/mL (micrograms per milliliter). SSRI stands for selective serotonin reuptake inhibitor.

3.4. Studies Investigating Non-GABA Neurobiological Mechanisms of Other Passiflora Species

This review compiled evidence for various neurobiological mechanisms of *Passiflora* species operating beyond the well-documented GABAergic system. Studies demonstrated direct modulation of the glutamatergic system, with isovitexin from *P. actinia* protecting against glutamate-induced excitotoxicity in hippocampal slices [16] and vitexin (found in *Passiflora*) inhibiting NMDA receptors (specifically NR2B subunits), reducing Ca^{2+} influx, and activating anti-apoptotic pathways in cortical neurons [17]. Additionally, evidence suggests HPA axis modulation, as a combined *P. caerulea* and *Melissa officinalis* extract reduced plasma corticosterone in stressed mice [12]. Flavonoids like chrysin (found in *P. caerulea*) and apigenin (found in *P. incarnata*, *P. foetida*, *P. subpeltata*) have been linked to non-sedating anxiolysis via central benzodiazepine receptors based on direct testing and cited prior research [3,11,12]. These diverse non-GABA targets and associated bioactive compounds are summarized in Table 3.

The modulation of monoaminergic pathways was also reported. Beta-carboline alkaloids (harmaline, harmine, harmalol) present in *P. incarnata* are known MAO-A inhibitors, and harmine also interacts with 5-HT2A receptors; these actions are thought to contribute to antidepressant-like behavioral effects observed following extract administration in mice [4]. The direct measurement of neurotransmitter levels after the chronic administration of a standardized *P. incarnata* extract revealed alterations in monoamine turnover and levels within specific rat brain structures, including increased spinal dopamine and decreased cerebellar norepinephrine, alongside changes in serotonin metabolism [14]. Furthermore, isoorientin isolated from *P. edulis f. flavicarpa* leaves produced antidepressant-like effects in mice, likely involving monoaminergic pathways, although not directly tested [15].

Investigations into analgesic mechanisms identified interactions with opioid and cholinergic systems. The antinociceptive effects of *P. incarnata* methanolic extract and an n-butanol fraction were significantly attenuated by the opioid antagonist naloxone in rodent models, implicating opioid receptor involvement potentially mediated by flavonoids, alkaloids, or oleamide [5,13]. The fatty acid amide oleamide, identified in high abundance in a *P. incarnata* extract, was also speculatively linked to cannabinoid CB1 receptor activity based on the existing literature, although direct antagonism was not performed in that specific study [5]. Furthermore, the analgesic activity of the *P. incarnata* n-butanol fraction was reversed by the nicotinic antagonist mecamylamine, suggesting engagement of nicotinic cholinergic pathways [13].

Mechanisms relevant to inflammation, oxidative stress, metabolic regulation, and the gut–brain axis were identified. A flavonoid-rich fraction from *P. foetida* fruits demonstrated anti-inflammatory activity in vitro by reducing pro-inflammatory cytokine production (NO, TNF-α, IL-6) and inhibiting MAPK, PI3K/Akt, and NF-κB signaling pathways in macrophages [19]. This fraction also beneficially modulated gut microbiota composition in an in vitro model [19]. Extracts from various *Passiflora* species (*P. subpeltata*, *P. edulis*, *P. alata*, *P.* sp.) containing compounds like quercetin, apigenin, gallic acid, catechin, β-carotene, and γ-tocopherol, along with general polyphenols/flavonoids, exhibit significant antioxidant activity, demonstrated through various in vitro assays like DPPH, ABTS, and metal chelation [20,22,23]. Anti-inflammatory activity for *P. subpeltata* was also shown in vivo through the reduction of paw edema, involving mediators like histamine, serotonin, kinins, and prostaglandins [22].

Table 3. Bioactive compounds in *Passiflora* species and their potential non-GABA neurobiological activities.

Bioactive Compound	***Passiflora* Species (Source)**	**Proposed Non-GABA Target**	**Supporting Study (Mechanism)**
Flavonoids (general), Oleamide	*P. incarnata* (Aerial parts)	Opioid receptors	Aman et al. (2016) [5]; Ingale and Kasture (2012) [13] (naloxone antagonism of analgesic effects in mice/rat models).
Oleamide	*P. incarnata* (Aerial parts)	Cannabinoid CB1 receptors (potential)	Aman et al. (2016) [5] (high oleamide content identified; link based on prior literature, not directly tested with antagonists in this study).
General extract constituents (with Melissa officinalis)	*P. caerulea* (Capsules, combined extract)	HPA Axis	Feliú-Hemmelmann et al. (2013) [12] (reduced plasma corticosterone in stressed mice).
Chrysin, Apigenin	*P. caerulea*, *P. incarnata*, *P. subpeltata*	Central benzodiazepine receptors (non-sedating anxiolysis)	Feliú-Hemmelmann et al. (2013) [12], Viola et al. (1995) [11] (citing prior research/direct testing showing selective binding and anxiolytic effect without sedation).
General extract constituents (Flavonoids implicated, e.g., Chrysin)	*P. incarnata* (Aerial parts, standardized extract)	Monoaminergic system (dopamine ↑ spinal cord, norepinephrine ↓ cerebellum, serotonin turnover altered)	Blecharz-Klin et al. (2024) [14] (HPLC measurement of neurotransmitters/metabolites in rat brain regions after chronic exposure).
Isovitexin	*P. actinia* (Leaves)	Glutamatergic system (neuroprotection against excitotoxicity)	dos Santos et al. (2016) [16] (protected mouse hippocampal slices from glutamate damage; effect linked to isovitexin).
Vitexin	Found in various *Passiflora* spp. (e.g., *P. incarnata*)	Glutamatergic system (NMDA receptor NR2B subunit downregulation, Ca^{2+} influx reduction)	Yang et al. (2014) [17] (neuroprotection against NMDA toxicity in cultured neurons via NR2B modulation).
Flavonoid-rich fraction (Orientin, Apigenin, Vitexin derivatives)	*P. foetida* (fruits)	Inflammatory pathways (MAPK, PI3K/Akt, NF-κB)	Han et al. (2023) [19] (reduced inflammatory markers in LPS-stimulated RAW264.7 cells).
Flavonoid-rich fraction (Orientin, Apigenin, Vitexin derivatives)	*P. foetida* (fruits)	Gut microbiota (modulation, increased SCFAs)	Han et al. (2023) [19] (altered microbial populations and increased SCFAs in BFBL dynamic gut simulator, relevant via gut-brain axis).
n-Butanol fraction components (Flavonoids, Alkaloids implicated)	*P. incarnata* (leaves)	Nicotinic acetylcholine receptors	Ingale and Kasture (2012) [13] (mecamylamine antagonism of analgesic effects in mice).
Beta-carboline alkaloids (Harmaline, Harmine, Harmalol)	*P. incarnata*	Serotonergic system (behavioral), MAO-A enzyme	Jafarpoor et al. (2014) [4] (antidepressant-like behavioral effects similar to SSRIs; known MAO-A inhibition by beta-carbolines).

Table 3. *Cont.*

Bioactive Compound	*Passiflora* Species (Source)	Proposed Non-GABA Target	Supporting Study (Mechanism)
Harmine	*P. incarnata*	Serotonin 5-HT2A receptors	Jafarpoor et al. (2014) [4] (citing prior research on direct binding).
Isoorientin	*P. edulis f. flavicarpa* (Leaves)	Pathways mediating antidepressant effects (likely monoaminergic)	Alves et al. (2020) [15] (antidepressant-like effect in forced swimming test in mice).
Acetone extract components (Quercetin, Apigenin, phenolics)	*P. subpeltata* (Leaves)	Inflammatory mediators (histamine, serotonin, prostaglandins, kinins), nociceptive pathways, prostaglandin synthesis	Saravanan et al. (2014) [22] (anti-inflammatory, analgesic, and antipyretic effects in vivo; antioxidant in vitro).
Polyphenols, Flavonoids, Carotenoids, Vitamin C	*P. edulis* (flavicarpa, edulis), *P. alata*, *P.* sp. (Fruit pulp)	Oxidative stress pathways (antioxidant activity)	Viera et al. (2022) [23]; Saravanan et al. (2014) [22] (correlation between polyphenol content and in vitro antioxidant assays; direct antioxidant assays).
Piceatannol (seed extract), β-carotene, γ-tocopherol (fruit extract)	*P. edulis* (seeds, fruit/pulp)	Lipid enzymes (lipase, esterase), inflammatory pathways (NO), vascular endothelium (eNOS/NO for vasodilation)	Sukketsiri et al. (2023) [20] (in vitro enzyme inhibition, reduced NO in macrophages, ex vivo vasodilation of aortic rings—cardiovascular/metabolic focus).
Standardized Extract	*P. incarnata*	HPA axis (clinical stress reduction), sleep regulation, cognitive function	Harit et al. (2024) [6] (clinical relevance: RCT showing improved stress scores, sleep metrics, and cognitive measures in humans).

Note: HPA axis stands for hypothalamic–pituitary–adrenal axis. Specific receptors mentioned are CB1 (cannabinoid receptor type 1), NMDA (N-methyl-D-aspartate), specifically its NR2B subunit, and the serotonin 5-HT2A receptor. Key signaling pathways include MAPK (mitogen-activated protein kinase), PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells). Enzymes discussed are MAO-A (monoamine oxidase A) and eNOS (endothelial nitric oxide synthase). Other terms include Ca^{2+} (calcium ion), LPS (lipopolysaccharide), SCFAs (short−chain fatty acids), BFBL (Bionic Fisogastrointestinal BioLogic dynamic gut simulator), NO (nitric oxide), SSRI (selective serotonin reuptake inhibitor), RCT (randomized controlled trial), and HPLC (high-performance liquid chromatography).

Cardiovascular effects were primarily explored using *P. edulis* extracts. An ethanolic seed extract (PSEE), high in piceatannol, exhibited a potent ex vivo vasodilation effect on rat aortic rings, significantly stronger than the effect observed with a fruit and pulp water extract (PFWE) containing β-carotene and γ-tocopherol [20]. This vasorelaxant activity is suggested to involve endothelial mechanisms, potentially including enhanced eNOS activity linked to piceatannol [20]. The PSEE also showed notable inhibition of pancreatic lipase and cholesterol esterase in vitro [20].

3.5. Structure, Distribution, and Biological Activity of Bioactive Compounds in Passiflora

The metabolite landscape of *Passiflora* can be grouped into recognizable scaffold families such as C-glycosyl flavones, aglycone flavones, stilbenes, β-carboline alkaloids, fatty-acid amides, carotenoids, and triterpene saponins [23,24]. Each family shows a preference for particular species and plant organs, information that guides both quality control and extraction strategy [18]. The main structural feature that sets each metabolite apart is listed together with the species and organ that provide the highest yield, and these details appear in Table 4.

Table 4. Chemistry and structural distribution of the main bioactive compounds in *Passiflora* species.

Metabolite/Class	Key Structural Motif/Distinguishing Feature	Species with Highest Reported Levels (Examples)	Plant Part Richest to Lower
Vitexin [16,17]	C-8 β-D-glucosyl-apigenin (C-glycosyl flavone); sugar is C-linked ⇒ hydrolysis-resistant yet polar	*P. incarnata*, *P. actinia*, *P. foetida*	Leaves ≫ tendrils > stems ≫ fruit rind
Isovitexin [16,24,25]	C-6 β-D-glucosyl-apigenin; sugar at C-6 twists B-ring dihedral angle vs. vitexin	*P. actinia* (very high), *P. edulis*, *P. cincinnata*	Leaves ≈ young shoots > flowers
Orientin/Isoorientin [15,18,24]	Luteolin C-glycosides (C-8 vs. C-6); extra 3′-OH (catechol) adds antioxidant power	*P. edulis f. flavicarpa*, *P. alata*	Leaves > peel > pulp
Chrysin and Apigenin (aglycone flavones) [22,26,27]	5,7-dihydroxy (chrysin) or 5,7,4′-trihydroxy (apigenin) flavone; no sugars ⇒ lipophilic	*P. caerulea*, *P. incarnata*, *P. subpeltata*	Flowers/aerial parts≫ roots
β-Carboline alkaloids * (harmine, harmaline, harman) [4,27]	Indolo [3,2-b]pyridine tricycle; N-9 basic centre; planar ⇒ BBB-permeant	*P. incarnata*, *P. alata*	Seeds > aerial parts
Piceatannol (stilbene) [20,28]	3,4,3′,5′-tetrahydroxystilbene; catechol B-ring boosts redox and enzyme inhibition vs. resveratrol	*P. edulis* (yellow and purple forms)	Seeds ≫ peel > pulp
Oleamide * [5,27]	cis-9-octadecenamide; C18:1 amide; very high logP (≈4.9)	*P. incarnata* (notably rich)	Aerial parts ≫ seeds
Carotenoids (β-carotene, lutein) [20,23,24]	C40 polyene chain with conjugated double bonds	*P. edulis*, *P. alata*, *P. quadrangularis*	Pulp ≥ peel ≫ leaves
Triterpene saponins (passiflorosides) [19,22]	Oleanane/ursane aglycone + sugar chains; amphiphilic surfactants	*P. subpeltata*, *P. foetida*	Leaves and stems > roots

Note: The column "Structural motif/feature" names the minimal element that distinguishes a metabolite from its nearest analogues. For instance, "C-8 β-D-glucosyl-apigenin" signals both the flavone core and its carbon-linked sugar, whereas "indolo [3,2-b]pyridine" identifies the tricyclic β-carboline scaffold. Listed species are the *Passiflora* taxa that phytochemical surveys report as the richest natural sources; the list is representative rather than exhaustive. Relative abundance within the plant is expressed semi-quantitatively; the symbol "≫" means "much greater than," ">" means "greater than," and "≥" means "slightly greater than." ≈ means roughly equivalent to. Rankings are derived from LC-MS or HPLC concentration data when available or from author-reported qualitative terms such as "rich" or "trace" when numerical values are lacking. * While these compounds are present in *P. incarnata*, the levels are generally very low in many commercial materials.

Leaf tissue emerges as the dominant reservoir for C-glycosyl flavones like vitexin and isovitexin, a pattern that fits their role in ultraviolet screening and oxidative defense during photosynthesis [16,17,25]. Seeds, in contrast, accumulate hydrophobic compounds that support embryo energy supply and antimicrobial protection, a role illustrated by the high piceatannol content of *P. edulis* [28]. Flowers and other aerial parts are enriched in lipophilic aglycone flavones such as chrysin and apigenin, which can influence pollinator signaling while remaining membrane-permeable [29].

Structural properties of these molecules hint at their pharmacokinetic behavior. The carbon linkage of the sugar in vitexin resists enzymatic cleavage; thus, the molecule gains polarity without losing planarity and can still cross the blood–brain barrier [17]. The indolo [3,2-b]pyridine nucleus of β-carbolines is planar and basic, favoring both blood–brain penetration and affinity for monoamine oxidase A [4]. Oleamide displays a very high logP value and an amide head group, which are properties that promote rapid membrane partitioning but also rapid first-pass hepatic metabolism, a point that must be considered in formulation work [5].

The major *Passiflora* scaffolds touch a surprisingly wide range of biological control points, from synaptic receptors to endothelial enzymes and from redox switches to membrane permeability [3,4,20,22]. By aligning each scaffold with its most convincing therapeutic focus and a succinct molecular explanation, the dataset condenses the diffuse literature into a clear pharmacodynamic landscape that readers can consult in Table 5.

Table 5. Biological targets and key mechanisms of the main bioactive compounds in *Passiflora* species.

Metabolite/Class	Lead Therapeutic/Biological Target	Key Molecular Mechanism
Vitexin [16,17]	Anti-excitotoxic/neuroprotective (NMDA/NR2B)	Down-regulates NR2B subunit, cuts glutamate-evoked Ca^{2+} influx and ROS; shifts Bcl-2: Bax towards survival
Isovitexin [16,24,25]	Neuroprotection and antioxidant back-up	Boosts γ-glutamyl transferase, preserves GSH, blocks mitochondrial ROS in glutamate-challenged hippocampal slices
Orientin/Isoorientin [15,18,24]	Anti-inflammatory, antioxidant, antidepressant	Catechol group scavenges ROS; activates Nrf2/HO-1; suppresses TNF-α and IL-6 via MAPK/PI3K/Akt; modulates monoamines in FST
Chrysin and Apigenin [22,26,27]	Non-sedating anxiolytic/anticonvulsant	Partial agonists at central BZ site of GABA-A; chrysin dampens CRH; apigenin antagonises TRPV1, adds antioxidant tone
β-Carbolines (harmine, harmaline, harman) [4,27]	Antidepressant and neurogenesis support	Reversible MAO-A inhibition ($IC_{50} \approx 0.3$ μM) → ↑ 5-HT/NE/DA; partial 5-HT_2A agonism; activates Wnt/β-catenin
Piceatannol [20,28]	Cardiometabolic/vascular antioxidant	Phosphorylates eNOS via PI3K/Akt → ↑ NO; inhibits pancreatic lipase and iNOS; potent superoxide scavenger
Oleamide [5,27]	Analgesic, sedative, sleep aid	Positive CB1 allosteric modulator; potentiates GABA-A currents; synergises with μ-opioid tone; promotes adenosine A_2A sleep signaling

Table 5. *Cont.*

Metabolite/Class	Lead Therapeutic/Biological Target	Key Molecular Mechanism
Carotenoids (β-carotene, lutein) [20,23,24]	Antioxidant and ocular/neuroprotection	Quench singlet-oxygen, halt lipid peroxidation; β-carotene → retinoic acid, engages nuclear RARs for neural repair
Triterpene saponins (passiflorosides) [19,22]	Permeability enhancer, anti-inflammatory	Amphiphilic surfactants improve co-metabolite uptake; block NF-κB translocation, down-regulate COX-2 and PLA_2

Note: HPA axis stands for hypothalamic–pituitary–adrenal axis. Receptor abbreviations include CB1 (cannabinoid receptor type 1), NMDA (N-methyl-D-aspartate glutamate receptor) with its NR2B subunit, and the serotonin 5-HT_2A receptor. Key signaling pathways are MAPK (mitogen-activated protein kinase), PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), and NF-κB (nuclear factor κ-light-chain-enhancer of activated B cells). Enzymes mentioned are MAO-A (monoamine oxidase A) and eNOS (endothelial nitric-oxide synthase). Additional terms include Ca^{2+} (calcium ion), NO (nitric oxide), RCT (randomized controlled trial), and HPLC (high-performance liquid chromatography).

A central motif emerging from this landscape is selective complementarity rather than redundancy. The polar C-glycosyl flavones are optimized for defending neural tissue against excitotoxic and inflammatory stress [16,17], whereas the planar, basic β-carbolines favor monoamine rescue and mood elevation [4]. Highly lipophilic molecules such as oleamide or the seed stilbene piceatannol pivot toward membrane-rich domains, with one modulating synaptic thresholds through CB1 and GABA-A cross-talk [5] and the other improving vascular tone and lipid metabolism [20]. Carotenoids and triterpene saponins add yet another layer, acting as systemic antioxidants or bioavailability enhancers rather than classical receptor ligands [18,22]. This pattern suggests that a full-spectrum extract, if standardized for relative scaffold abundance, could achieve balanced multitarget coverage without the pharmacodynamic clashes that often plague polypharmacy.

Equally remarkable is the way structural quirks predict downstream behavior. A carbon-linked sugar keeps vitexin polar enough for systemic circulation while planar enough to slip into the brain in modest amounts [17]. The indolo [3,2-b]pyridine core of β-carbolines confers both blood–brain permeability and high affinity for the flavin cofactor pocket of monoamine oxidase A [4]. Oleamide's very high logP ensures that it embeds rapidly in neuronal membranes, facilitating the allosteric modulation of both cannabinoid and GABAergic channels but also demanding careful formulation to manage first-pass metabolism [5].

4. Discussion

Traditional use and early pharmacological work on *Passiflora*, especially *P. incarnata*, framed its anxiolytic and hypnotic properties almost exclusively in terms of GABA-A receptor modulation, often attributed to flavonoids acting as benzodiazepine site partial agonists [3,11]. Our synthesis confirms that perspective but also shows that it is only a fragment of a far more intricate neuropharmacological picture. Across well-studied species such as *P. incarnata*, *P. caerulea*, *P. actinia*, *P. foetida*, *P. edulis*, *P. subpeltata*, and *P. tenuifila* [30], the genus engages opioid, cholinergic, monoaminergic, and glutamatergic networks; attenuates oxidative and inflammatory stress; modulates the HPA axis; and influences metabolic and vascular functions, effects that may partly converge via gut–brain communication. Recognizing this multidimensional footprint is essential for rational bench-to-bedside development.

4.1. Modulation of the Glutamatergic System and Neuroprotection

Isovitexin isolated from *P. actinia* protects mouse hippocampal slices against glutamate-induced damage, whereas vitexin blocks NR2B-containing NMDA receptors and limits Ca^{2+} influx in cortical neurons [16,17]. Together, these findings illustrate complementary strategies for reducing excitotoxicity that operate independently of the classic GABA pathway. Chronic administration of a standardized *P. incarnata* extract lowers basal hippocampal glutamate and aspartate in vivo [14,31]. Overall, C glycosyl flavones such as isovitexin and vitexin provide a clear mechanistic basis for the neuroprotective reputation of *Passiflora* species by directly restraining excessive glutamatergic activity.

4.2. Modulation of Monoaminergic Pathways (Serotonin, Dopamine, Norepinephrine)

Prolonged *P. incarnata* treatment increases spinal dopamine, decreases cerebellar norepinephrine, and accelerates serotonin turnover, all of which parallel its anxiolytic and antidepressant-like behavioral effects [31]. β-Carboline alkaloids including harmine, harmaline, and harmalol are potent MAO-A inhibitors and also interact with 5-HT_2A receptors, thereby adding a further antidepressant component [4]. Leaf fractions of *P. edulis* that are rich in isoorientin show selective serotonin re-uptake inhibitor level efficacy in the forced-swim test without affecting locomotion, confirming the importance of C glycosyl flavones in mood regulation [15].

4.3. Engagement of Opioidergic and Cholinergic Systems in Analgesia

Naloxone only partially reverses the antinociceptive effects produced by methanolic and n-butanol fractions of *P. incarnata*, implicating opioid receptors in the analgesic action of the plant [5,13]. The same n-butanol fraction becomes ineffective after pretreatment with mecamylamine, which points to an independent nicotinic cholinergic mechanism [13]. Evidence for both pathways distinguishes *Passiflora*-based analgesia from classical non-steroidal anti-inflammatory drugs and suggests value in mixed neuropathic and inflammatory pain.

4.4. Anti-Inflammatory and Antioxidant Mechanisms

A flavonoid-rich fraction from *P. foetida* fruit suppresses LPS-induced nitric oxide, tumor necrosis factor alpha, and interleukins six and one beta, while blocking MAPK, PI3K-Akt, and NF-κB signaling in macrophages [19]. Polyphenols from *P. subpeltata* leaves and from *P. edulis* seeds and pulp scavenge reactive oxygen species, chelate transition metals, and activate the Keap1–Nrf2 antioxidant pathway; in stressed rodents, *P. incarnata* reduces malondialdehyde, confirming in vivo relevance [5,20,22]. The convergence of antioxidant and anti-inflammatory activities helps protect neural tissue from cytokine-driven oxidative injury.

4.5. Neuroprotection, Anti-Inflammation, Antioxidation, and HPA Axis Control

Infusion of *P. caerulea* during immobilization stress lowers corticosterone surges in mice, and a randomized clinical trial demonstrated that *P. incarnata* capsules significantly reduce perceived stress in humans [6,12]. Additional rodent studies link normalized corticosterone to improved anxiety-like behavior [31]. These results indicate that *Passiflora* acts as a phytotherapeutic modulator of the hypothalamic–pituitary–adrenal axis, which is a central link between psychological stress, neuroinflammation, and mood disorders.

Anti-inflammatory and neuroprotective actions are robust. A flavonoid-rich *P. foetida* fraction inhibits MAPK, PI3K/Akt, and NF-κB activation, reducing TNF-α and IL-6 in LPS-stimulated macrophages [19]. *P. incarnata* dampens stress-induced TNF-α/IL-1β surges [5], and *P. edulis* leaf extract suppresses IL-8 in inflamed Caco-2 monolayers [32].

P. caerulea extracts attenuate seizures and cognitive decline in epileptic mice by limiting oxidative damage [26]. Considering the significant inflammatory burden and neurological sequelae associated with conditions such as bacterial meningitis [33], the anti-inflammatory properties of *Passiflora* species may hold adjunct therapeutic promise in mitigating long-term neuroinflammation-related damage.

Antioxidant capacity is equally pervasive. *P. edulis* activates the Keap1–Nrf2 axis and scavenges ROS, which are actions traced to seed piceatannol and juice phenolics such as gallic acid [20,34]. Leaves of *P. subpeltata* and *P. incarnata* exhibit strong radical-quenching and metal-chelating activity owing to quercetin, apigenin, and catechin [22]. In vivo, *P. incarnata* reduces malondialdehyde accumulation in stressed rodents [5].

Stress and HPA axis regulation translate to behavior and clinical outcomes. Chronic *P. incarnata* lowers corticosterone and anxiety-like behaviors in rodents [31]. Extracts of *P. edulis* and *P. caerulea* similarly suppress stress-evoked corticosterone spikes [12]. Randomized trials demonstrate that *P. incarnata* reduces perioperative anxiety as effectively as benzodiazepines but with fewer cognitive or motor side effects [27,35] and improves perceived stress, sleep, and vasomotor symptoms [6,36].

4.6. Emerging Mechanisms: Gut–Brain Axis and Metabolic Effects

Flavonoids from *P. foetida* reshape gut microbiota composition and enhance short-chain fatty acid production in a dynamic fermentation model, suggesting that microbial changes may contribute to neurochemical modulation [29]. *P. edulis* seed extract, rich in piceatannol, promotes endothelium-dependent vasodilation and inhibits pancreatic lipase and cholesterol esterase, effects that could integrate cerebrovascular protection with weight control [20]. *P. edulis* leaf extract restores epithelial barrier integrity in inflamed Caco-2 cultures [32], and *P. cincinnata* pectin promotes probiotic growth [25,37]. These emerging findings indicate that *Passiflora* influences peripheral systems such as the gut and metabolism, which in turn feed back to brain function and broaden the therapeutic scope beyond direct neurotransmission.

Cardiometabolic effects are spearheaded by *P. edulis*. Seed piceatannol drives endothelium-dependent vasodilation and inhibits digestive lipases [20]. Peel and leaf preparations improve glycemic control, counteract diabetic nephropathy, and exhibit antiplatelet properties [38,39]. Juice phenolics confer myocardial protection [34]. Such vascular and metabolic benefits may secondarily safeguard cerebral perfusion and reduce neurovascular risk.

4.7. Translational Outlook

The converging evidence for the modulation of opioid, cholinergic, monoaminergic, and glutamatergic systems, combined with HPA-axis normalization, anti-inflammatory and antioxidant neuroprotection, and gut–brain engagement, gives *Passiflora* a coherent mechanistic rationale for treating complex neuropsychiatric and systemic disorders [40]. Controlled trials of *P. incarnata* already support its use for perioperative anxiety, chronic stress, and sleep disturbance, with exploratory signals in menopausal symptoms and substance-use disorders [6,27,35,41].

Although *P. incarnata* dominates clinical investigations, other species offer distinctive chemotypes and bioactivities. *P. edulis* combines seed piceatannol, leaf C-glycosyl flavonoids (vitexin, isoorientin), and pulp carotenoids to yield antioxidant, antidepressant, and cardiometabolic actions [1,15,20]. *P. actinia* supplies isovitexin but also cataleptogenic constituents [37]; *P. caerulea* offers chrysin and neuroprotection [26,42,43]; *P. foetida* couples apigenin with microbiota modulation [19]; and *P. subpeltata* excels in polyphenol-driven anti-inflammation [22]. The genus harbors flavonoids, stilbenes, β-carbolines, saponins,

carotenoids, phenolic acids, and terpenes [19,24,44], a diversity shaped by glandular morphology [45] and ecological pressures [45,46]. Synergistic interplay—for example, between MAO-A-inhibiting β-carbolines, GABA-A/NMDA-active flavonoids, antioxidant stilbenes, and oleamide—may underpin both efficacy and tolerability.

Yet, key translational gaps persist. Large, rigorously designed clinical studies integrating pharmacokinetics, biomarkers, and defined chemotypes are needed to confirm efficacy, refine dosing, and map drug–herb interactions. Standardization is critical, as phytochemical profiles vary with genotype, environment [47], endophytic microbiota [48], and plant health [49]. Safety surveillance must continue, particularly regarding cataleptogenic species (*P. actinia*) and potential cytochrome interactions [50]. Leveraging under-explored species [1] and sustainable by-products [29,39,51] may unlock new therapeutic avenues. A multitarget phytotherapeutic such as *Passiflora* could ultimately complement or even outperform single-receptor drugs where polypharmacy or pleiotropic pathophysiology prevail.

4.8. Limitations

While the evidence for non-GABAergic mechanisms is compelling, some limitations exist in the current literature. Many studies rely on preclinical in vivo and in vitro models, necessitating careful translation to humans. There is considerable heterogeneity in the *Passiflora* species used, extraction methods, dosages, and administration protocols, making direct comparisons difficult. This inherent variability across studies should be kept in mind when interpreting synthesized findings, as it complicates direct comparisons and pooling of results. Furthermore, some mechanisms, such as MAO-A inhibition and cannabinoid system involvement, were inferred based on phytochemical content or behavioral effects rather than being directly demonstrated with specific molecular tools.

5. Conclusions

Future research could examine head-to-head comparisons of different species and standardized extracts. Mechanistic studies using specific receptor antagonists/agonists, binding assays, and genetic models are warranted to confirm receptor interactions and downstream signaling pathways. Pharmacokinetic studies mapping the absorption, distribution, metabolism, and excretion of key active compounds (e.g., flavonoids, alkaloids, oleamide) are important. Research exploring the synergistic interactions between different non-GABA pathways, and between non-GABA and GABAergic mechanisms, would be particularly valuable. Finally, clinical trials are required that incorporate biomarkers relevant to these non-GABA pathways (e.g., inflammatory markers, HPA axis hormones, neurotransmitter metabolites, neuroimaging) to definitively link these mechanisms to therapeutic outcomes in humans for conditions ranging from anxiety and sleep disorders to pain, depression, and cognitive support. Such research will solidify the understanding of *Passiflora*'s complex pharmacology and optimize its therapeutic applications beyond simple GABA modulation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biochem5030021/s1, Table S1: Search strategy adapted to each platform; Table S2: Excluded full-text articles; Table S3: Risk of bias assessment; Table S4: PRISMA checklist.

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