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Therapeutic Potential of Vitexin and Isovitexin in Central Nervous System Disorders: A Preclinical Systematic Review

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ABSTRACT

Central nervous system (CNS) disorders are complex conditions involving oxidative stress, neuroinflammation, and neurotransmitter imbalance, necessitating the development of multi-target therapeutic strategies. Plant-derived flavonoids such as vitexin (apigenin-8-C-glucoside) and isovitexin have gained increasing attention due to their potential neuroprotective properties. This preclinical systematic review evaluates the therapeutic potential of these compounds in CNS disorders. A comprehensive literature search was conducted across PubMed, Scopus, ScienceDirect, SpringerLink, and Google Scholar for studies published between January 2000 and April 2023, including *in-vitro* and *in-vivo* experimental investigations assessing neuroprotective, anticonvulsant, antidepressant, anxiolytic, and anti-neurodegenerative effects. A total of 20 studies met the inclusion criteria, predominantly involving *in-vivo* animal models. The findings indicate that vitexin and isovitexin exert significant neuroprotective effects through antioxidant activity, modulation of neuroinflammatory pathways, regulation of neurotransmitter systems, and inhibition of neuronal apoptosis. Beneficial outcomes were consistently observed in experimental models of epilepsy, depression, anxiety, ischemic brain injury, and Alzheimer's disease. However, the available evidence is limited to preclinical studies with variable methodological quality and absence of clinical data. In conclusion, vitexin and isovitexin demonstrate promising multi-target neuroprotective potential, but further clinical validation and safety evaluation are required to support their therapeutic application in humans.

Keywords: Vitexin; isovitexin; central nervous system disorders; neuroprotection; flavonoids; neurodegeneration.

1. INTRODUCTION

The central nervous system (CNS), consisting of the brain and spinal cord, is responsible for coordinating complex physiological processes including cognition, sensory perception, motor function, and emotional regulation. Disorders affecting the CNS represent a significant global health challenge due to their high prevalence, chronic nature, and substantial socioeconomic burden.

Neurological and psychiatric disorders such as epilepsy, depression, anxiety, Parkinson's disease, and Alzheimer's disease contribute significantly to disability and mortality worldwide. According to recent global health estimates, neurological disorders account for a substantial proportion of disability-adjusted life years (DALYs), highlighting the urgent need for improved therapeutic strategies and preventive approaches.[1,2]

Many CNS disorders are associated with multifactorial pathogenic mechanisms including oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, and dysregulation of

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neurotransmitter systems.[2] These processes can lead to neuronal damage, synaptic dysfunction, and progressive neurodegeneration. Current pharmacological treatments for neurological and psychiatric conditions often provide symptomatic relief but may be limited by adverse effects, drug resistance, or insufficient efficacy in preventing disease progression.[3,4] Consequently, there has been increasing interest in identifying novel therapeutic agents, particularly those derived from natural products, which may target multiple molecular pathways simultaneously.

Plant-derived phytochemicals have attracted considerable attention as potential therapeutic agents for neurological disorders due to their diverse biological activities and relatively favorable safety profiles. Among these, flavonoids represent an important class of naturally occurring polyphenolic compounds widely distributed in fruits, vegetables, and medicinal plants. Numerous studies have demonstrated that flavonoids exhibit antioxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties, which may contribute to their beneficial effects in neurological diseases.[5-7] These compounds have been shown to modulate signaling pathways involved in neuronal survival, synaptic plasticity, and neuroinflammation.

Vitexin (apigenin-8-C-glucoside) is a naturally occurring flavone glycoside commonly found in several medicinal plants such as *Passiflora incarnata*, *Crataegus* species, *Vitex negundo*, and *Desmodium* species. It has been widely investigated for its diverse pharmacological properties including antioxidants, anti-inflammatory, anti-cancer, cardioprotective, and neuroprotective activities. Experimental studies have demonstrated that vitexin can modulate multiple signaling pathways associated with neuronal injury, including the regulation of oxidative stress, inhibition of inflammatory mediators, and suppression of apoptosis. These mechanisms suggest that vitexin may play a protective role against various CNS disorders.[8,9]

Isovitexin, a structural isomer of vitexin, is another naturally occurring flavonoid that has attracted growing interest due to its biological activities. Like vitexin, isovitexin has been reported to possess antioxidant, anti-inflammatory, and neuroprotective effects.[10] Emerging evidence suggests that isovitexin may influence neuronal signaling pathways, improve synaptic plasticity, and attenuate neuroinflammatory responses associated with neurodegenerative diseases. Preclinical studies have also reported potential beneficial effects of isovitexin in experimental models of anxiety, depression, and cognitive impairment.[11]

Recent investigations have explored the potential role of vitexin and isovitexin in several CNS-related conditions including epilepsy, depression, anxiety disorders, ischemic brain injury, and neurodegenerative diseases such as Alzheimer's disease. These studies suggest that the neuroprotective effects of these flavonoids may be mediated through mechanisms involving regulation of neurotransmitters, inhibition of oxidative stress, modulation of inflammatory pathways, and protection against neuronal apoptosis.[12,13] Additionally, the ability of vitexin to cross the blood–brain barrier further enhances its potential as a candidate molecule for the treatment of neurological disorders.[14,15]

Despite increasing experimental evidence supporting the neuroprotective potential of vitexin and isovitexin, the available literature remains scattered across different experimental models and disease conditions. A comprehensive synthesis of current evidence is therefore necessary to better understand the therapeutic relevance of these phytochemicals in CNS disorders and to identify potential research gaps for future investigations.

Therefore, the objective of the present systematic review is to summarize and critically evaluate the existing literature on the pharmacological effects of vitexin and isovitexin in CNS disorders. The review focuses on experimental and preclinical studies with particular emphasis on their mechanisms of action, neuroprotective properties, and potential therapeutic applications in neurological diseases.

2. MATERIALS & METHODS

2.1 Study Design

This study is a systematic review of preclinical evidence evaluating the neuroprotective and therapeutic effects of vitexin and isovitexin in central nervous system (CNS) disorders. The review includes *in-vivo* animal studies and *in-vitro* experimental models and was conducted in accordance with PRISMA guidelines. The primary objective was to assess the pharmacological efficacy, mechanisms of action, and safety-related implications of these phytochemicals within the

context of drug vigilance and alternative therapeutic strategies.

2.2 Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies published between January 2000 and April 2023. Multiple electronic databases, including PubMed/MEDLINE, Scopus, ScienceDirect, SpringerLink, and Google Scholar, were systematically searched. The search strategy was developed using a combination of Medical Subject Headings (MeSH) and free-text keywords related to vitexin, isovitexin, and central nervous system (CNS) disorders (Fig. 1).

The PubMed/MEDLINE search strategy was structured as follows: ("Vitexin"[Title/Abstract] OR "apigenin-8-C-glucoside" [Title/Abstract] OR "Isovitexin" [Title/Abstract]) AND ("central nervous system" [Title/Abstract] OR "CNS disorders" [Title/Abstract] OR "epilepsy" [Title/Abstract] OR "seizure" [Title/Abstract] OR "depression" [Title/Abstract] OR "anxiety" [Title/Abstract] OR "Alzheimer disease" [Title/Abstract] OR "neurodegeneration" [Title/Abstract]). This strategy was adapted for other databases using appropriate syntax, field tags, and Boolean operators to ensure optimal sensitivity and specificity. All searches were limited to studies published in English within the specified time frame.

Eligible studies were restricted to preclinical experimental research, including both *in-vivo* animal studies and *in-vitro* cellular or molecular investigations. Most included studies utilized rodent models, particularly mice and rats, to evaluate the neuropharmacological effects of vitexin and isovitexin in CNS disorders such as epilepsy, depression, anxiety, ischemic brain injury, and neurodegenerative diseases. No human clinical studies met the inclusion criteria, reflecting the early-stage translational status of these compounds in neurotherapeutics.

2.3 Eligibility Criteria

Studies identified through the search process were screened according to predefined inclusion and exclusion criteria.

2.3.1 Inclusion Criteria

Studies were included if they met the following criteria:

- Articles published between January 2000 and April 2023.
- Original research articles.
- Studies investigating vitexin or isovitexin in relation to CNS disorders.
- Experimental studies including in vitro, *in-vivo*, or preclinical models.
- Articles published in the English language.
- Studies evaluating pharmacological activities such as neuroprotective, anticonvulsant, antidepressant, anxiolytic, or anti-neurodegenerative effects.

2.3.2 Exclusion Criteria

The following studies were excluded:

- Review articles, editorials, commentaries, and conference abstracts.
- Studies not related to CNS disorders.
- Articles lacking sufficient experimental or methodological details.
- Studies investigating compounds other than vitexin or isovitexin.
- Duplicate publications across databases.

2.4 Study Selection Process

All retrieved records were imported into a reference management system, and duplicated articles were removed. The remaining studies were screened in two stages:

- Title and abstract screening to determine relevance.
- Full-text evaluation to confirm eligibility based on the predefined inclusion and exclusion criteria.

Two independent reviewers performed the screening process. Discrepancies between reviewers were resolved through discussion and consensus.

2.5 Data Extraction

Data extraction was conducted independently by two reviewers using a standardized data extraction form and cross verified to ensure accuracy and consistency. The following information was collected from each including study:

- Author and year of publication
- Study design
- Experimental model (*in-vitro* or *in-vivo*)
- Source of vitexin or isovitexin
- Dose or concentration used
- CNS disorder investigated
- Key pharmacological outcomes
- Proposed mechanisms of action

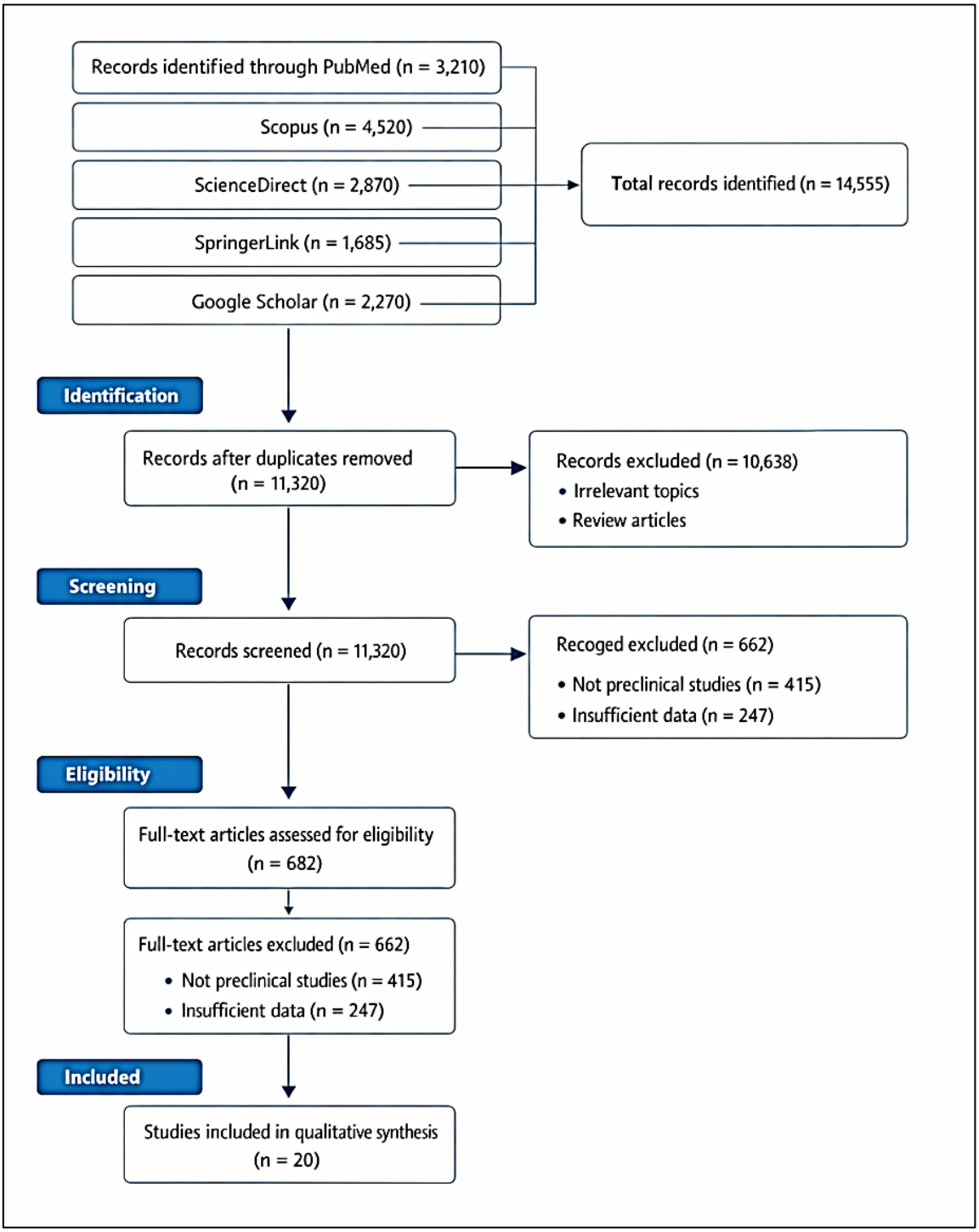

Fig. 1: Flow diagram of literature search and study selection (PRISMA)

2.6 Risk of Bias Assessment

The risk of bias assessment revealed that most included studies had unclear or high risk of bias, primarily due to insufficient reporting of randomization, allocation concealment, and blinding procedures.

Attrition bias was generally low, while reporting bias could not be excluded in several studies. Overall, the methodological quality of the included preclinical studies was moderate to low.

2.7 Data Synthesis and Analysis

Due to the heterogeneity in experimental models, outcome measures, and study designs, a qualitative synthesis of the findings was performed rather than a quantitative meta-analysis. The results were categorized according to the type of CNS disorder investigated, including:

- Anti-epileptic activity
- Antidepressant activity
- Anxiolytic activity

- Neuroprotective effects in neurodegenerative diseases

The findings were summarized and presented in tables and descriptive narrative format to facilitate comparison between studies.

3. RESULTS

3.1 Study Selection

The systematic database search identified 14,555 records from PubMed/MEDLINE, Scopus, ScienceDirect, SpringerLink, and Google Scholar for the period January 2000 to April 2023. After title/abstract screening and full-text retrieval of potentially relevant articles, 682 studies were assessed for eligibility. Of these, 662 full-text articles were excluded because they did not meet the predefined inclusion criteria, and 20 studies were included in the qualitative synthesis. The included evidence was exclusively preclinical and comprised *in-vivo* animal models and *in-vitro* experimental studies.

The main reasons for exclusion at the full-text stage included lack of direct relevance to CNS disorders, evaluation of compounds other than vitexin or isovitexin, non-original article types such as reviews or editorials, and insufficient experimental or methodological detail for data extraction and qualitative synthesis.

3.2 Study Characteristics

The included studies were exclusively preclinical and comprised both *in-vitro* and *in-vivo* experimental designs. Most studies (approximately 75–80%) utilized *in-vivo* rodent models, including mice and rats, while a smaller proportion involved cellular models.

Animal models employed across studies included pentylenetetrazole (PTZ)-induced seizures, pilocarpine-induced epilepsy, forced swimming test (FST), tail suspension test (TST), elevated plus maze (EPM), ischemia/reperfusion injury models, and Alzheimer's disease models. These models were used to evaluate anticonvulsant, antidepressant, anxiolytic, neuroprotective, and cognitive-enhancing effects.

Interventions varied considerably, with some studies utilizing purified vitexin or isovitexin, while others employed plant extracts containing these compounds. This heterogeneity introduces variability in pharmacological interpretation and limits direct comparability between studies.

3.3 Source of Intervention: Pure Compound vs Plant Extract

A critical distinction among the included studies is the use of either purified vitexin/isovitexin or plant-derived extracts containing these compounds. Several studies employed crude or semi-purified plant extracts, including Passiflora incarnata, Euterpe oleracea, and other flavonoid-rich sources, where vitexin was one of multiple bioactive constituents.

In contrast, a limited number of studies investigated isolated vitexin or isovitexin, allowing for more precise attribution of pharmacological effects. The use of complex plant extracts introduces potential confounding due to synergistic or additive effects of other phytochemicals.

Therefore, the observed therapeutic effects cannot be exclusively attributed to vitexin or isovitexin in all studies, representing an important limitation in the analysis of preclinical evidence.

3.4 Risk of Bias Assessment

The methodological quality of included animal studies was assessed using the SYRCLE risk of bias tool (Table 1). Overall, the included studies demonstrated moderate to high risk of bias. Most studies did not report random sequence generation selection bias. Blinding of investigators and outcome

Table 1: Risk of bias assessment of included animal studies using the SYRCLE tool

Bias Domain	Risk Level	Description
Selection Bias (Sequence Generation)	Unclear / High	Randomization methods not reported in most studies
Allocation Concealment	Unclear	No information provided on allocation procedures
Baseline Characteristics	Low	Most studies reported comparable baseline groups
Performance Bias (Blinding)	High	Lack of blinding in animal handling and treatment
Detection Bias (Outcome Assessment)	Unclear / High	Blinding of outcome assessors rarely reported
Attrition Bias	Low	Outcome data generally complete
Reporting Bias	Unclear	Selective reporting cannot be excluded
Other Bias	Moderate	Variability in dosing, extract composition, and models

Note: Overall Risk of Bias: Moderate to High

assessors were rarely described, contributing to performance and detection bias. Attrition bias was generally low, as most studies reported complete outcome data; however, selective reporting could not be excluded.

Additionally, variability in experimental design, dosing regimens, and use of plant extracts introduced further methodological heterogeneity. Importantly, the presence of moderate-to-high risk of bias suggests that the reported therapeutic effects of vitexin and isovitexin may be overestimated, and findings should therefore be interpreted with caution.

3.5 Anti-Epileptic Activity

Epilepsy is a chronic neurological disorder characterized by recurrent seizures caused by abnormal neuronal excitability. Globally, epilepsy affects more than 50 million individuals and represents a significant neurological health burden. Several molecular mechanisms contribute to epileptogenesis, including oxidative stress, neuroinflammation, mitochondrial dysfunction, and imbalance between excitatory glutamatergic and inhibitory GABAergic neurotransmission. Natural flavonoids have received increasing attention as potential anticonvulsant agents due to their neuroprotective and antioxidant properties.[16]

Vitexin (apigenin-8-C-glucoside) has been extensively investigated in experimental epilepsy models. Preclinical studies have demonstrated that vitexin exerts anticonvulsant effects in pentylenetetrazole (PTZ), pilocarpine, and maximal electroshock seizure models. The compound significantly delays seizure onset, reduces seizure severity, and improves survival in experimental animals. These effects are believed to be mediated through increased GABAergic neurotransmission, suppression of oxidative stress, and modulation of inflammatory mediators.

Vitexin also has been reported to restore altered levels of neurotransmitters such as GABA and glutamate, inhibit lipid peroxidation, and increase endogenous antioxidant enzymes including superoxide dismutase (SOD) and glutathione (GSH) in brain tissue. Collectively, these mechanisms contribute to the observed neuroprotective and anticonvulsant effects of vitexin.[18,20]

3.6 Anti-Depressant Activity

Depression is one of the most prevalent psychiatric disorders, characterized by persistent low mood, anhedonia, cognitive impairment, and disturbances in sleep and appetite. The pathophysiology of depression involves complex mechanisms including monoaminergic neurotransmitter imbalance, neuroinflammation, oxidative stress, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, and reduced neurotrophic signaling. Conventional antidepressant therapies, such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants, are effective for many patients but may produce adverse effects and delayed therapeutic response.[6]

Natural flavonoids have attracted considerable attention for their potential antidepressant effects due to their antioxidant, anti-inflammatory, and neuroprotective properties. Vitexin (apigenin-8-C-glucoside), a naturally occurring flavone glycoside found in several medicinal plants including *Passiflora incarnata*, *Crataegus pinnatifida*, and *Euterpe oleracea*, has demonstrated promising antidepressant-like activity in experimental models.

Preclinical studies have shown that vitexin reduces depressive-like behavior in animal models such as the forced swimming test (FST) and tail suspension test (TST). These behavioral paradigms measure behavioral despair and are widely used for evaluating antidepressant efficacy. Administration of vitexin significantly reduced immobility time in these tests, indicating antidepressant-like effects comparable to standard antidepressant drugs.

The antidepressant activity of vitexin appears to involve several neurobiological mechanisms, including modulation of monoaminergic neurotransmission, enhancement of serotonergic and dopaminergic signaling, reduction of oxidative stress, and regulation of brain-derived neurotrophic factor (BDNF) expression. Additionally, vitexin has been reported to modulate inflammatory mediators and improve neuronal plasticity, further supporting its potential therapeutic value in depressive disorders.[3,24]

The reviewed evidence suggests that vitexin and vitexin-containing plant extracts may exert antidepressant effects through multitarget neuroprotective mechanisms, making them promising candidates for further investigation as alternative or adjunctive therapies for depression.

3.7 Anxiolytic Activity

Anxiety disorders are among the most prevalent neuropsychiatric conditions, characterized by

excessive fear, apprehension, and behavioral disturbances. The underlying pathophysiology involves dysregulation of neurotransmitter systems, particularly gamma-aminobutyric acid (GABA), serotonin (5-HT), and dopamine, along with oxidative stress and neuroinflammatory processes.[14,15]

Vitexin and isovitexin have demonstrated significant anxiolytic effects in various preclinical models. The elevated plus maze (EPM) and open field test (OFT) are widely used behavioral paradigms to evaluate anxiety-related responses in rodents. Administration of vitexin has been shown to increase the time spent in open arms and the number of entries into open arms in EPM, indicating reduced anxiety-like behavior.[25] These behavioral effects are comparable to standard anxiolytic agents such as diazepam.

The anxiolytic activity of vitexin is primarily attributed to its modulation of the GABAergic system, particularly through interaction with the GABA-A receptor complex. This mechanism is like benzodiazepines but may offer a more favorable safety profile with reduced sedative and dependency-related effects.[19] Additionally, vitexin influences serotonergic and dopaminergic neurotransmission, which further contributes to its anxiolytic properties.

Oxidative stress plays a critical role in the development of anxiety disorders. Vitexin exhibits potent antioxidant activity by scavenging reactive oxygen species and enhancing endogenous antioxidant defenses such as superoxide dismutase and glutathione. These effects protect neuronal cells from stress-induced damage and improve behavioral outcomes.[8] Vitexin-rich medicinal plants such as *Passiflora incarnata* have been traditionally used in the management of anxiety and insomnia. Experimental studies have confirmed that extracts containing vitexin significantly reduce anxiety-related behaviors without causing major motor impairment.[19,25]

The available evidence suggests that vitexin and isovitexin possess promising anxiolytic potential through multimodal mechanisms, including neurotransmitter modulation, antioxidant effects, and neuroprotection. However, clinical studies are lacking, and further research is required to establish their safety, efficacy, and therapeutic applicability in humans.

3.8 Neuroprotective Effects on Ischemic Brain Injury

Ischemic brain injury, commonly associated with stroke, results from reduced cerebral blood flow leading to neuronal death, oxidative stress, excitotoxicity, and inflammation. Restoration of blood flow often exacerbates injury through reperfusion-induced oxidative damage and apoptosis.[1]

Vitexin has demonstrated significant neuroprotective effects in experimental models of cerebral ischemia/reperfusion injury. Studies indicate that vitexin reduces infarct size, improves neurological function, and attenuates neuronal apoptosis.[2] These protective effects are mediated through modulation of key signaling pathways, including inhibition of mitogen-activated protein kinase (MAPK) pathways and suppression of oxidative stress.

Additionally, vitexin has been shown to regulate hypoxia-inducible factor-1α (HIF-1α), thereby reducing hypoxia-induced neuronal injury.[3] Its antioxidant properties contribute to reduced lipid peroxidation and preservation of mitochondrial function, which are critical in ischemic conditions. Vitexin exhibits promising neuroprotective potential in ischemic brain injury by targeting multiple pathological mechanisms.

3.9 Anti-Alzheimer's Activity

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by β-amyloid (Aβ) plaque accumulation, tau protein aggregation, oxidative stress, and neuroinflammation.[5]

Vitexin has demonstrated potential therapeutic effects in AD models by inhibiting Aβ aggregation and reducing its cytotoxicity.[6] It also modulates cholinergic neurotransmission by inhibiting acetylcholinesterase activity, thereby improving acetylcholine levels and cognitive function.

Furthermore, vitexin reduces neuroinflammatory mediators and oxidative stress, both of which are critical contributors to AD progression. Experimental studies have shown that vitexin improves spatial memory and learning in animal models, suggesting its potential role in preventing cognitive decline.

Table 2: Summary of included preclinical studies evaluating vitexin and isovitexin in CNS disorders

S. No.	Activity	Study Model	Species	Intervention	Source	Dose	Mechanism	Outcome & Reference
1	Anti-epileptic	PTZ-induced seizure model	Swiss albino mice	Extract	Desmodium triflorum	800 mg/kg	Antioxidant, GABA modulation	Delayed seizure onset and reduced duration[16]
2	Anticonvulsant	Pilocarpine-induced epilepsy	Mice	Pure compound	Apigenin-8-C-glucoside	10 mg/kg	NMDA receptor modulation	Reduced seizure severity and restored neurotransmitters[17]
3	Anticonvulsant	PTZ seizure model	Rodents	Extract	Euterpe oleracea	Not specified	Antioxidant effect	Increased seizure latency[12]
4	Anticonvulsant	Seizure model	Rats	Pure compound	Vitexin	Not specified	Anti-apoptotic, antioxidant	Reduced neuronal damage[18]
5	Anticonvulsant	Epilepsy model	Rodents	Extract	Passiflora incarnata	150–600 mg/kg	GABAergic modulation	Reduced seizure severity[21]
6	Anticonvulsant	Seizure model	Mice	Extract	Lavandula stoechas	600 mg/kg	CNS depressant activity	Reduced PTZ seizures[20]
7	Antidepressant	Forced swimming test	Mice	Extract	Passiflora edulis	25–50 mg/kg	Monoaminergic modulation	Reduced immobility time[24]
8	Antidepressant	Behavioral model	Rodents	Pure compound	Vitexin	300–500 mg/kg	Serotonergic/dopaminergic pathways	Improved depressive behavior[6]
9	Antidepressant	FST model	Mice	Extract	Euterpe oleracea	Not specified	Antioxidant, anti-inflammatory	Reduced depressive behavior[3]
10	Anxiolytic	Elevated plus maze	Mice	Extract	Passiflora incarnata	5 mg/kg	GABA-A receptor modulation	Increased open-arm time[25]
11	Anxiolytic	Behavioral model	Rodents	Pure compound	Vitexin	Not specified	GABAergic modulation	Reduced anxiety-like behavior[19]
12	Anxiolytic	Open field test	Rodents	Extract	Flavonoid-rich extract	Not specified	Antioxidant activity	Improved locomotion[15]
13	Neuroprotection	Ischemia/reperfusion model	Mice	Pure compound	Vitexin	Not specified	MAPK pathway inhibition	Reduced infarct size[11]
14	Neuroprotection	Hypoxia model	Rats	Pure compound	Vitexin	Not specified	HIF-1α inhibition	Reduced brain injury[10]

15	Anti-Alzheimer's	Aβ-induced model	Neuronal cells	Extract	Lawsonia inermis	Not specified	Anti-amyloid activity	Inhibited amyloid aggregation[13]
16	Cognitive enhancement	Morris water maze	Rats	Pure compound	Vitexin	Not specified	BDNF upregulation	Improved spatial memory[2]
17	Cognitive enhancement	Cognitive model	Rodents	Extract	Flavonoid extract	Not specified	Neurotrophic modulation	Increased synaptic plasticity[4]
18	Anti-inflammatory	Experimental model	Rodents	Pure compound	Vitexin	Not specified	Anti-inflammatory pathways	Reduced TNF-α and IL-6[7]
19	Antioxidant	Brain model	Rodents	Pure compound	Vitexin	Not specified	Antioxidant defense	Increased SOD and GSH[4]
20	Neuroprotection	Seizure model	Rodents	Extract	Plant-derived vitexin	Not specified	Antioxidant, anti-inflammatory	Reduced oxidative stress[14]

Note: CNS = Central Nervous System; PTZ = Pentylenetetrazole; FST = Forced Swimming Test; TST = Tail Suspension Test; EPM = Elevated Plus Maze; OFT = Open Field Test; SOD = Superoxide Dismutase; GSH = Glutathione; TNF-α = Tumor Necrosis Factor-alpha; IL-6 = Interleukin-6; BDNF = Brain-Derived Neurotrophic Factor; MAPK = Mitogen-Activated Protein Kinase; HIF-1α = Hypoxia-Inducible Factor-1 alpha.

Doses are reported as described in the original studies. "Extract" refers to plant-derived preparations containing vitexin or isovitexin, while "pure compound" refers to isolated forms of these flavonoids.

3.10 Cognitive and Memory Enhancement

Cognitive impairment and memory deficits are common features of neurodegenerative and psychiatric disorders. These impairments are often associated with oxidative stress, synaptic dysfunction, and reduced neurotrophic support.

Vitexin has shown significant cognitive-enhancing effects in experimental models. Studies indicate that vitexin improves spatial learning and memory performance in behavioral tests such as the Morris water maze.[8] These effects are attributed to increased expression of brain-derived neurotrophic factor (BDNF) and improved synaptic plasticity.

Also, vitexin enhances cholinergic function by increasing acetylcholine levels and inhibiting acetylcholinesterase activity. This mechanism is particularly relevant in cognitive disorders such as Alzheimer's disease.

3.11 Antioxidant and Anti-inflammatory Neuroprotection

Oxidative stress and neuroinflammation are central mechanisms in the pathogenesis of CNS disorders. Excess production of reactive oxygen species (ROS) leads to lipid peroxidation, protein damage, and neuronal apoptosis.[1]

Vitexin exhibits potent antioxidant activity by scavenging free radicals and enhancing endogenous antioxidant systems such as superoxide dismutase (SOD) and glutathione (GSH).[4] It also inhibits lipid peroxidation and preserves cellular integrity. In addition, vitexin exerts anti-inflammatory effects by suppressing pro-inflammatory cytokines such as TNF-α and IL-6 and inhibiting microglial activation. These combined effects contribute to its neuroprotective properties across multiple CNS disorders.

3.12 Strength of Evidence

The overall strength of evidence was considered low to moderate due to the preclinical nature of the included studies, variability in experimental models, and methodological limitations identified through risk of bias assessment. The absence of clinical validation further limits the translational applicability of the findings.

4. DISCUSSION

This preclinical systematic review provides a comprehensive synthesis of current experimental evidence on the neuropharmacological effects of vitexin and isovitexin in central nervous system (CNS) disorders. The findings demonstrate that these flavonoids exert consistent neuroprotective, anticonvulsant, antidepressant, and anxiolytic effects across multiple *in-vivo* and *in-vitro* models. Importantly, the observed therapeutic effects are mediated through a convergence of molecular mechanisms targeting oxidative stress, neuroinflammation, neurotransmitter dysregulation, and apoptotic pathways, which are widely recognized as central contributors to CNS pathology.[5-7]

A key strength of the included studies is the consistent demonstration of pleiotropic pharmacological activity. Unlike conventional CNS drugs that typically act on single molecular targets, vitexin and isovitexin exhibit multi-target modulation, influencing interconnected signaling pathways involved in neuronal survival and function. This characteristic is particularly relevant given the multifactorial nature of neurological disorders, where oxidative stress, mitochondrial dysfunction, inflammatory cascades, and synaptic dysregulation coexist and interact dynamically.[3,4] The ability of these flavonoids to simultaneously modulate these processes suggests a potential advantage over conventional therapies that may fail to address disease complexity.

In epilepsy models, vitexin demonstrated robust anticonvulsant activity, particularly in pentylenetetrazole (PTZ) and pilocarpine-induced seizure paradigms. The reduction in seizure frequency, delayed onset, and improved survival outcomes observed across studies are strongly associated with enhancement of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission and restoration of excitatory–inhibitory balance.[16,17] In addition, vitexin significantly attenuated oxidative stress markers and neuronal damage, indicating a dual role in both seizure suppression and neuroprotection. This is clinically relevant, as many currently available antiepileptic drugs are associated with neurotoxicity and do not provide disease-modifying benefits.

Similarly, the antidepressant and anxiolytic effects observed in rodent behavioral models such as the forced swimming test, tail suspension test, and elevated plus maze are indicative of significant modulation of monoaminergic and GABAergic systems. Vitexin has been shown to enhance serotonergic and dopaminergic signaling while also influencing brain-derived neurotrophic factor

(BDNF) expression, which plays a critical role in neuroplasticity and synaptic remodeling.[6,24] These findings suggest that vitexin may exert antidepressant-like effects through mechanisms that overlap with those of conventional antidepressants, while potentially offering a more favorable safety profile due to its natural origin and lower risk of dependency compared to benzodiazepines.

In the context of neurodegenerative diseases, particularly Alzheimer's disease, vitexin demonstrated the ability to inhibit β-amyloid aggregation, reduce neuroinflammatory responses, and enhance cholinergic neurotransmission. These mechanisms are highly relevant to disease pathogenesis, as amyloid toxicity, oxidative stress, and inflammation are key drivers of neuronal degeneration.[4] Furthermore, improvements in cognitive function and memory performance observed in behavioral models such as the Morris water maze support the potential role of vitexin as a cognitive enhancer and neuroprotective agent. These findings are significant given the limited efficacy of current pharmacotherapies in halting or reversing neurodegenerative progression.

The neuroprotective effects of vitexin in ischemic brain injury models further highlight its therapeutic potential. Experimental studies have demonstrated that vitexin reduces infarct size, attenuates neuronal apoptosis, and improves neurological outcomes following ischemia/reperfusion injury. These effects are mediated through modulation of mitogen-activated protein kinase (MAPK) signaling pathways, inhibition of hypoxia-inducible factor-1α (HIF-1α), and reduction of oxidative stress.[10,11] Such multi-pathway modulation is particularly advantageous in ischemic injury, where secondary damage due to reperfusion-induced oxidative stress significantly contributes to neuronal loss.

A unifying feature across all CNS conditions reviewed is the potent antioxidant and anti-inflammatory activity of vitexin and isovitexin. These compounds enhance endogenous antioxidant defense systems, including superoxide dismutase and glutathione, while simultaneously reducing lipid peroxidation and pro-inflammatory cytokine production such as tumor necrosis factor-α and interleukin-6.[7,8] Given the growing recognition of oxidative stress and neuroinflammation as common pathological denominators across CNS disorders, these findings provide a strong mechanistic basis for the broad therapeutic applicability of these flavonoids.

From a translational perspective, caution is warranted when extrapolating these findings to human populations. Animal models, while valuable for mechanistic insights, do not fully replicate the complexity of human CNS disorders. Differences in metabolism, pharmacokinetics, and disease progression may significantly influence therapeutic outcomes. Furthermore, many studies utilized high experimental doses that may not be clinically achievable, raising concerns regarding dose translation and safety.

Several limitations must be considered when interpreting the findings of this review. The relatively small number of included studies reflects the strict inclusion criteria applied, particularly the focus on specific flavonoids (vitexin and isovitexin) and preclinical CNS models. This approach enhances the specificity and relevance of the findings but may limit the breadth of available evidence. First, all included studies were preclinical, limiting direct translation to human clinical settings. Second, significant heterogeneity was observed in experimental models, dosing regimens, and outcome measures. Third, many studies utilized plant extracts rather than isolated compounds, introducing potential confounding effects. Additionally, methodological limitations, including lack of randomization and blinding, increase the risk of bias and may lead to overestimation of therapeutic effects. Publication bias cannot be excluded, as studies with positive findings are more likely to be published. Finally, insufficient data are available regarding pharmacokinetics, long-term safety, and drug–herb interactions, which are critical for clinical translation.

Future research should prioritize the generation of high-quality translational evidence to bridge the gap between preclinical findings and clinical application. Well-designed randomized controlled trials are essential to establish the efficacy and safety of vitexin and isovitexin in human populations, while comprehensive pharmacokinetic studies are needed to determine optimal dosing strategies, bioavailability, and central nervous system penetration. The development of standardized formulations with defined phytochemical composition will be critical to ensure reproducibility and regulatory compliance. In parallel, advanced

drug delivery systems, including nanotechnology-based approaches, may enhance targeted CNS delivery and therapeutic efficacy. Furthermore, future investigations should focus on elucidating molecular targets through omics-based approaches such as transcriptomics and proteomics to better characterize underlying mechanisms of action. The exploration of combination therapies with existing CNS drugs may also provide valuable insights into potential synergistic effects and strategies for minimizing drug-related toxicity. Overall, the adoption of standardized experimental protocols and rigorous methodological design will be essential to strengthen the reliability and translational relevance of future studies.

5. CONCLUSION

Vitexin and isovitexin are promising plant-derived flavonoids that demonstrate significant multi-target neuroprotective effects across a range of central nervous system disorders, including epilepsy, depression, anxiety, ischemic brain injury, and neurodegenerative diseases. Evidence from preclinical studies indicates that these compounds act through modulation of oxidative stress, neuroinflammation, neurotransmitter systems, and apoptotic pathways, supporting their potential as integrative therapeutic agents. However, the current body of evidence is limited to *in-vitro* and *in-vivo* experimental models with variable methodological quality, and there is a notable absence of clinical validation. Critical gaps remain in pharmacokinetic characterization, bioavailability, long-term safety, and standardization of formulations. Therefore, while vitexin and isovitexin represent promising candidates for future neuropharmacological development, their translation into clinical practice will require well-designed clinical trials, rigorous safety evaluation, and standardized therapeutic approaches.

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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