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Review Article

Bioelectrical and Neurochemical Modulation by *Peganum harmala*: A Narrative Review of its Role in Neural Hyperactivity, Stress Circuitry, and Cortical Excitability

Abdullah Faisal Albukhari*

Department of Medicine, Faculty of Medicine, King Abdulaziz University, Rabigh, SAUDI ARABIA.

ABSTRACT

Neuropsychiatric and neurodegenerative conditions are widespread across the globe, frequently linked to disturbances in monoaminergic transmission, increased cortical excitability, and maladaptive responses to stress. Existing pharmacological treatments are often hindered by delayed onset of action, limited effectiveness, and adverse side effects. This narrative review provides a critical examination of the neurochemical and electrophysiological characteristics of *Peganum harmala* L. (Syrian rue), highlighting its potential as a versatile botanical option for managing Central Nervous System (CNS) disorders. A comprehensive literature review was performed utilizing databases such as PubMed, Scopus, and Web of Science until 2025. This search included preclinical studies, mechanistic investigations, and toxicological assessments concerning key alkaloids from *P. harmala* (harmine, harmaline, tetrahydroharmine, vasicine). Only studies published in English that reported pharmacological or electrophysiological findings were considered. The β-carboline alkaloids found in *P. harmala* function as reversible inhibitors of MAO-A, leading to increased levels of serotonin, dopamine, and norepinephrine. Harmine has been shown to enhance BDNF expression while also exhibiting antioxidant properties. On an electrophysiological level, harmaline modifies thalamocortical rhythms and EEG patterns, affecting cortical excitability. In animal models, it demonstrates anxiolytic, antidepressant, and neuroprotective effects; however, at high doses it can provoke proconvulsant activity and serotonergic toxicity. Its role in modulating stress through HPA axis downregulation and amygdala-hippocampal plasticity further emphasizes its significance in psychiatry. Conclusion: *Peganum harmala* presents a distinctive dual mechanism-both biochemical and bioelectrical-that positions it as a potential treatment for mood disorders, seizures, and stress-related conditions. However, successful clinical application will require standardized formulations along with studies focusing on dosage safety and controlled trials to confirm effectiveness while minimizing neurotoxicity.

Keywords: *Peganum harmala*, β-carbolines, Harmine, MAO-A inhibition, BDNF, EEG, Cortical excitability, Neuropharmacology, Electrophysiology, Stress modulation.

Correspondence:
Mr. Abdullah Faisal Albukhari
Department of Medicine, Faculty of Medicine, King Abdulaziz University, Rabigh-25732, SAUDI ARABIA.
Email: aabdulqaderalbukhari@stu.kau.edu.sa
ORCID: 0009-0004-1482-4411

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INTRODUCTION

Neuropsychiatric and neurodegenerative disorders pose a significant and growing challenge to global health, leading to long-term disabilities, diminished quality of life, and rising healthcare costs. The Global Burden of Disease Study identifies major depressive disorder, anxiety disorders, and schizophrenia as primary contributors to years lived with disability on a worldwide scale.[1-3] Additionally, the prevalence of neurodegenerative conditions like Alzheimer's and Parkinson's diseases is rapidly increasing, driven by aging populations and the absence of effective curative treatments.[4,5] Despite progress in psychopharmacology and neurology, existing treatment options for neuropsychiatric disorders often fall short. Antidepressants and antipsychotic medications frequently exhibit delayed efficacy, limited effectiveness, resistance to treatment, and troublesome side effects such as metabolic syndrome, extrapyramidal symptoms, and sexual dysfunction[6-8] Moreover, many synthetic medications focus on individual neurotransmitter systems without addressing the intricate neural circuits and neurochemical interactions that characterize these conditions.[9]

These drawbacks have sparked an intensified search for alternative or supplementary therapies derived from natural products that offer multi-target effects with favorable safety profiles. Various plant-based compounds have demonstrated potential in influencing Central Nervous System (CNS) activity through

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different mechanisms including monoamine oxidase inhibition, antioxidant properties, and modulation of neurotransmitter systems.[10-13] Notably, *Peganum harmala* L., commonly referred to as Syrian rue, has garnered attention for its high alkaloid content-particularly harmine and harmaline-which are known for their psychoactive and neuromodulatory characteristics.[14-17] The traditional use of *Peganum harmala* spans numerous cultures where it has been utilized for its calming properties in spiritual practices as well as in treating nervous system disorders.[7,10] Contemporary pharmacological research has validated its effects on serotonergic, dopaminergic, GABAergic, and glutamatergic pathways while also recognizing its function as a reversible inhibitor of Monoamine Oxidase A (MAO-A).[8,14,18,19] Recent studies have started investigating its bioelectrical impact on cortical excitability and seizure models; however, these areas remain insufficiently explored.[9,20] Given this distinctive profile that integrates neurochemical influence with potential electrophysiological modulation-*Peganum harmala* emerges as a promising subject for further investigation. This narrative review aims to thoroughly explore the neurobiological impacts of *Peganum harmala* with particular emphasis on its effects on neural hyperactivity, stress circuitry dynamics, and cortical excitability while highlighting existing gaps in electrophysiological and behavioral research evidence.

BOTANICAL AND ETHNOPHARMACOLOGICAL OVERVIEW OF *PEGANUM HARMALA*

Botanical Identity and Taxonomy

Peganum harmala L., commonly referred to as Syrian rue, is a perennial herbaceous species within the Nitrariaceae family, previously categorized under Zygophyllaceae.[21-23] This plant is distinguished by its slender, deeply lobed foliage, white blossoms, and seed pods rich in β-carboline alkaloids, especially harmine and harmaline.[24-26] It flourishes in arid to semi-arid environments and shows resilience in saline soils, making it common in both steppe and desert habitats.

Traditional Uses

Various traditional medicinal systems have employed *P. harmala* for its neuroactive, antispasmodic, and antimicrobial effects. It features prominently in Unani and Persian medicine for ailments such as hysteria, epilepsy, depression, and other disorders affecting the nervous system.[27,28] The seeds are frequently smoked or burned for their fragrance and purported calming properties; decoctions derived from the plant are used to address rheumatic conditions and gastrointestinal issues.[29,30] Additionally, folk medicine sometimes utilizes the plant as an emmenagogue or abortifacient;[31] however, these applications pose significant toxicological risks and are not advised in contemporary phytotherapy[32-34] Caution is warranted against overstating these traditional applications without pharmacological support since exaggerated folkloric claims-such as those involving protection against malevolent spirits-do not adhere to scientific criteria.[35,36]

Distribution and Cultural Relevance

In several traditional societies, particularly in parts of North Africa and the Middle East, *Peganum harmala* has been culturally used in rituals believed to offer protection from perceived harm, including what is referred to as the "evil eye." These practices have been transmitted across generations and are widely regarded as part of regional heritage.[7-9,37] While belief in the l societies, particularly in parts of North Africa and the Middle East, *Peganum harmala* has been culturally used in rituals believed to offer protection from perceived harm, including ws, and focuses solely on the pharmacological and neurophysiological aspects of the plant.[11,15,20,38]

Standardization and Safety Concerns

Despite its extensive ethnopharmacological background, *Peganum harmala* raises notable safety issues. Its β-carboline alkaloids can function as reversible inhibitors of Monoamine Oxidase-A (MAO-A), leading to potential interactions with serotonergic drugs that could result in hypertensive crises or serotonin syndrome if not managed appropriately.[39-42] Moreover, at elevated doses, harmaline and harmine may produce neurotoxic side effects such as tremors, hallucinations, and seizures in experimental models.[32,43]

The standardization of *P. harmala* extracts is currently constrained due to variations in alkaloid levels across different geographic regions and plant parts.[15] Modern pharmacognosy underscores the necessity for precise dosing practices, stringent quality control measures, and public awareness regarding both its risks and therapeutic windows.[17,37]

PHYTOCHEMISTRY OF *PEGANUM HARMALA*

Peganum harmala L. is a prominent medicinal herb recognized for its abundant indole alkaloid content, especially β-carbolines. These compounds have been the subject of extensive research due to their neuroactive, antioxidant, and monoamine oxidase inhibitory effects, which render them of considerable pharmacological relevance.

Major Alkaloids

The seeds and roots of *P. harmala* are notably rich in β-carboline alkaloids, including:

- Harmine.
- Harmaline.
- Tetrahydroharmine.
- Harmalol.

- Vasicine (a quinazoline alkaloid also present in Adhatoda vasica).

Harmine and harmaline are the primary alkaloids found in the seeds, often comprising more than 3% of their weight.[44-46] These substances serve as reversible inhibitors of Monoamine Oxidase A (MAO-A) and significantly influence serotonergic and dopaminergic neurotransmission.[47-49]

Structural Classes

The alkaloids derived from *P. harmala* can be categorized into two principal structural groups:

β-carbolines: This category consists of harmine, harmaline, harmalol, and tetrahydroharmine, all stemming from the tricyclic β-carboline framework. They are synthesized via the Pictet–Spengler condensation pathway using tryptophan as a precursor.[50-52]

Quinazoline alkaloids: This group includes vasicine and vasicinone, which differ structurally and pharmacologically from β-carbolines and are associated with bronchodilatory and uterotonic effects.[53,54]

Methods of Isolation and Characterization

The extraction of major alkaloids typically employs acid-base extraction followed by chromatographic methods such as Thin-Layer Chromatography (TLC), High-Performance Liquid Chromatography (HPLC), or Gas Chromatography-Mass Spectrometry (GC-MS).[55-59] Detection and quantification of these alkaloids usually involve techniques such as UV-visible spectrophotometry, NMR spectroscopy, and Electrospray Ionization Mass Spectrometry (ESI-MS).[60,61]

For instance, the purity and identity of harmine and harmaline extracted from seeds have been validated through a combination of column chromatography and ^1H-NMR spectroscopy.[62-64]

Concentration in Various Plant Parts

The distribution of alkaloids varies among different parts of the plant:

Seeds: The most concentrated source, with total alkaloid levels between 2-6% dry weight, primarily consisting of harmine and harmaline.[44,65,66]

Roots: Exhibit lower concentrations mainly comprising derivatives such as harmalol and harmaline.[8]

Stems and leaves: Contain minimal amounts that fluctuate significantly based on growth stage and environmental factors.[67]

Factors like geographic origin, soil conditions, and harvesting time also affect the concentration ratios of β-carbolines; hence standardization is essential for their pharmacological applications.[68] Table 1 presents an overview of the key alkaloids extracted from *Peganum harmala*, detailing their chemical classifications, neuropharmacological actions, and therapeutic benefits as supported by current preclinical research.

NEUROCHEMICAL MODULATION

The pharmacological effects of *Peganum harmala* are fundamentally linked to its ability to modulate central neurochemical pathways through various mechanisms. Its β-carboline alkaloids influence Monoamine Oxidase (MAO), monoaminergic neurotransmitters, and both GABAergic and glutamatergic systems, as well as neurotrophic and antioxidant signaling, which contribute to its potential in neuropsychiatric applications.

Monoamine Oxidase Inhibition

Harmine and harmaline, the predominant β-carbolines found in *Peganum harmala*, are effective reversible inhibitors of monoamine oxidase A (MAO-A).[8,59,65] This mitochondrial enzyme plays a crucial role in the oxidative deamination of serotonin (5-HT), Norepinephrine (NE), and Dopamine (DA)-neurotransmitters essential for mood regulation.

By blocking MAO-A activity, these β-carbolines enhance the synaptic availability of these monoamines, paralleling the pharmacodynamics seen with contemporary antidepressants and anxiolytics.[69,70] Preclinical studies have confirmed that harmine exhibits antidepressant-like properties in models such as the forced swim test and tail suspension test, demonstrating efficacy comparable to that of conventional antidepressants.[71-73]

Furthermore, harmine has been observed to restore monoaminergic equilibrium in models of chronic stress, underscoring its significance for conditions related to depression, anxiety, and neurodegeneration associated with reduced monoamine levels.[49,74]

Modulation of Neurotransmitters

In addition to inhibiting MAO-A, the alkaloids from *P. harmala* appear to directly influence monoaminergic transmission. Research involving rodent models indicates that harmaline elevates serotonin and dopamine concentrations within the hippocampus and prefrontal cortex-regions crucial for emotional regulation and cognitive processes.[7,8]

Moreover, harmine enhances norepinephrine release in the locus coeruleus, further supporting its effects on arousal and depression alleviation.[10] These alterations in neurotransmitter levels depend on dosage and often coincide with behavioral modifications such as increased locomotor activity or reduced immobility in animal models indicative of mood disorders.[18,75-77]

Interaction with GABA and NMDA Systems

Recent findings suggest that *P. harmala* also engages with GABAergic and glutamatergic pathways. Notably, harmaline boosts GABA transmission potentially by influencing GABA-A receptors; this contributes to its anticonvulsant and anxiolytic properties.[78]

Simultaneously, β-carbolines may inhibit NMDA receptors, thus mitigating glutamate-induced excitotoxicity-a critical factor involved in epilepsy as well as neurodegenerative diseases under chronic stress conditions.[79-81] This dual mechanism (enhanced GABA function plus NMDA inhibition) fosters a neuroprotective environment by curbing excitotoxic cascades while maintaining an inhibitory balance-helping explain the anti-seizure and anti-anxiety effects attributed to *P. harmala* extracts.[82-84]

Neurotrophic and Antioxidant Mechanisms

Harmine along with other related β-carbolines has shown an ability to upregulate Brain-Derived Neurotrophic Factor (BDNF), which is vital for synaptic plasticity, neuronal survival, and cognitive performance.[85] In experiments using mouse models, treatment with harmine significantly raised BDNF mRNA and protein levels within the hippocampus-effects similar to those observed with Selective Serotonin Reuptake Inhibitors (SSRIs).[71]

Additionally, *P. harmala* displays antioxidant characteristics by decreasing lipid peroxidation levels while increasing glutathione peroxidase activity and reducing Reactive Oxygen Species (ROS) in neurons subjected to oxidative stress.[9,15,86] Such actions may provide protective benefits against neurodegenerative disorders like Alzheimer's disease and Parkinson's disease where oxidative imbalance is a core pathological concern.[87,88]

BIOELECTRICAL MODULATION AND CORTICAL EXCITABILITY

Although the neurochemical effects of *Peganum harmala* have been fairly well understood, its bioelectrical impacts-especially regarding cortical Excitability and Electroencephalographic (EEG) activity-have only recently come under investigation. These electrophysiological characteristics serve as an essential functional counterpart to its neuropharmacological properties and may elucidate its role in various neurological disorders, including epilepsy, Attention-Deficit/Hyperactivity Disorder (ADHD), and stress-related conditions. A visual depiction of the diverse neuropharmacological effects of *Peganum harmala* is shown in Figure 1, highlighting its influence on neurotransmission, cortical excitability, and potential therapeutic applications.

Effects on EEG Patterns

Multiple studies have indicated that harmaline, a primary β-carboline found in *P. harmala*, modifies EEG activity in animal models. Specifically, harmaline triggers rhythmic tremor-like discharges and enhances low-frequency power (theta and delta) within cortical areas.[44,89-92] Such oscillations are believed to signify improved synchronization among cortical neurons, a phenomenon frequently observed in hyperexcitable states like epilepsy and essential tremor.

Administering harmaline to rats resulted in bilateral spike-wave discharges, which align with increased cortical excitability and heightened seizure vulnerability[48] Importantly, these effects were dependent on dosage and were reversible, indicating that extracts from *P. harmala* may present both proconvulsant and anticonvulsant properties based on context and dosage.

Experimental Models of Cortical Excitability

In rodent studies, harmaline has served as a tool for inducing tremors and seizure-like phenomena, making it valuable for examining neuroexcitation and oscillatory behavior.[89,93] Administering harmaline via intraperitoneal injection generates synchronous bursts within the inferior olive, thereby influencing the cerebello-thalamo-cortical circuits-essential pathways involved in generating tremors and regulating attention.[94]

Additionally, long-term EEG monitoring of mice treated with harmaline revealed sporadic paroxysmal discharges, reinforcing the idea that harmala alkaloids directly affect thalamocortical rhythms.[95] These experimental models hold significant translational promise for understanding conditions such as absence seizures and essential tremors.

Implications in Epilepsy, ADHD, and Stress

The influence on cortical excitability presents various potential clinical implications:

In the case of epilepsy-particularly generalized absence seizures-the capacity of harmaline to synchronize spike-wave activity could shed light on new mechanisms underlying seizure generation and modulation.[96]

For ADHD patients, changes in thalamocortical activity along with elevated theta power have been observed; this might theoretically be impacted by the EEG-modulating properties of *P. harmala*.[97,98]

In stress-related disorders characterized by irregular synchrony and heightened cortical responsiveness-often associated with imbalanced glutamate and GABA signaling-the oscillatory entrainment induced by harmala could stabilize these abnormalities while contributing to its noted anxiolytic effects.[7,77]

Role in Thalamo-Cortical Feedback Loops

A particularly fascinating aspect of harmaline's mechanism is how it affects thalamo-cortical feedback loops. These circuits play a vital role in managing consciousness, sensory processing, motor coordination, and attentional focus. Harmaline has been shown to amplify rhythmic activity within these networks by enhancing

output from the inferior olive-which sends excitatory signals to both the thalamus and cortex through the cerebellum.[89,94,99]

This rhythmic synchronization is thought to reorganize oscillatory dynamics particularly within theta and alpha frequency bands critical for attentional gating as well as sensory integration.[100,101] Disruption of these loops has been linked to both neurodevelopmental disorders as well as neurodegenerative diseases-underscoring the therapeutic potential offered by targeted modulation strategies. Table 2 provides an overview of electrophysiological results concerning *P. harmala* alkaloids, emphasizing patterns of cortical excitability and their possible significance for neurological conditions.

MODULATION OF STRESS CIRCUITRY

Psychiatric disorders related to stress, such as depression, anxiety, and Post-Traumatic Stress Disorder (PTSD), are significantly linked to the dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis along with its associated neural pathways. The bioactive substances found in *Peganum harmala*, especially β-carbolines like harmine and harmaline, have demonstrated beneficial effects in regulating neuroendocrine and behavioral responses to stress in preclinical studies.

Effects on the HPA Axis: CRH, ACTH, Cortisol

The HPA axis is activated by stress through the release of Corticotropin-Releasing Hormone (CRH) from the hypothalamus, followed by the secretion of Adrenocorticotropic Hormone (ACTH) from the pituitary gland and cortisol release from the adrenal cortex. Chronic activation of this system is associated with hippocampal damage as well as anxiety and mood disorders.[102,103]

Research indicates that harmine reduces corticosterone levels-analogous to cortisol in rodents-in models induced by stress, demonstrating a downregulatory effect on hyperactivity within the HPA axis.[104,105] This modulation may be attributed to the inhibition of MAO-A, which enhances serotonergic activity while suppressing CRH expression in the hypothalamus.[106,107]

Neural Substrates: Hippocampus, Amygdala, Prefrontal Cortex

Studies utilizing neuroimaging and histological techniques have pinpointed the hippocampus, amygdala, and Prefrontal Cortex (PFC) as critical areas impacted by chronic stress. These regions contain a high density of glucocorticoid receptors and are vulnerable to structural and functional damage when subjected to elevated cortisol levels.[69,108,109]

Preclinical research shows that administering harmine increases BDNF expression in both the hippocampus and PFC, thereby

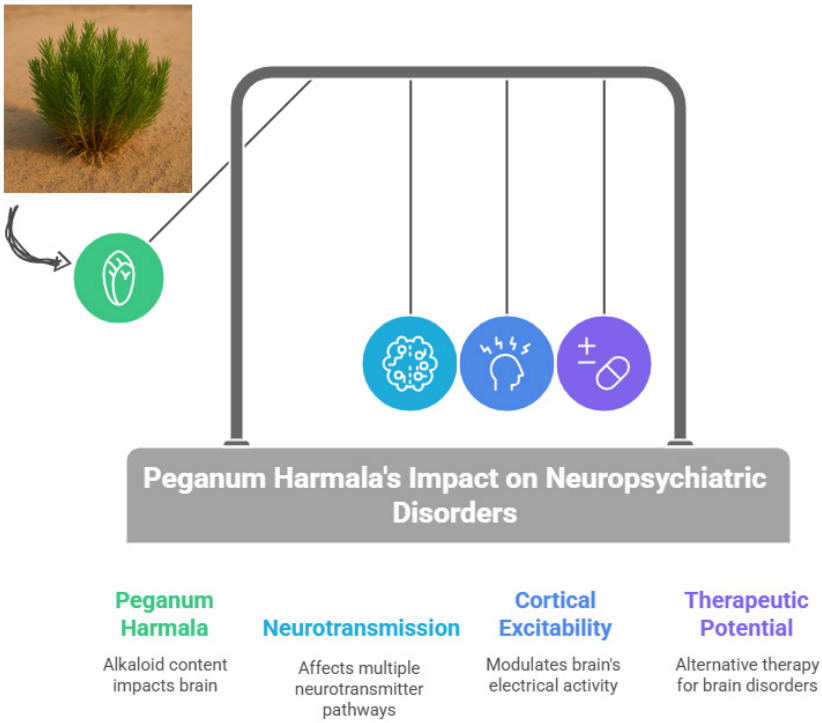

Figure 1: Overview of the effects of *Peganum harmala* on neuropsychiatric disorders, emphasizing its alkaloid composition, modulation of neurotransmitter pathways, impact on cortical excitability, and possibilities for therapeutic application.

promoting neurogenesis and enhancing synaptic plasticity.[71,110,111] In addition to this, harmine seems to normalize neuronal excitability within the amygdala-a central hub for processing fear and anxiety-potentially through its effects on GABAergic and glutamatergic signaling pathways.[112,113]

Behavioral Evidence: Forced Swim, Tail Suspension, Open Field

Behavioral assessments conducted on rodents have yielded strong evidence supporting the stress-reducing effects of *P. harmala* alkaloids. In tests such as the Forced Swim Test (FST) and Tail Suspension Test (TST), harmine significantly lowered immobility time-a measure indicative of antidepressant efficacy.[7,38] These results were comparable to those achieved with standard Selective Serotonin Reuptake Inhibitors (SSRIs) and exhibited a dose-dependent relationship.

In Open Field Tests (OFT), harmine was observed to enhance exploratory behavior while increasing time spent in central areas-indicative of reduced anxiety-like behaviors without causing hyperactivity.[8,114] Importantly, these outcomes were diminished when serotonergic receptors were blocked, reinforcing the notion that serotonergic mechanisms mediate harmine's anxiolytic effects.[85,115]

Role in Stress-Induced Hyperactivity and Neuroplasticity

Chronic stress is known for disrupting hippocampal neurogenesis, impairing synaptic plasticity, and fostering neuronal hyperexcitability-all contributing factors for cognitive deficits and emotional disturbances.[49,69,116] Harmine appears capable of reversing these adverse effects by stimulating neurotrophic signaling pathways such as BDNF-TrkB while also activating anti-oxidative mechanisms.[111,117]

Furthermore, harmine influences electrophysiological responses during stress by diminishing cortical spike frequencies and stabilizing excitatory-inhibitory balance; this may elucidate its function in mitigating behavioral sensitization resulting from stressors.[46,118]

These findings indicate that *P. harmala*-with its β-carboline alkaloids-serves as a multi-faceted modulator for both endocrine systems and neuronal responses related to stress conditions. This suggests significant therapeutic promise for addressing depression, anxiety disorders, and PTSD.

TOXICOLOGICAL PROFILE

Although *Peganum harmala* exhibits promising pharmacological properties, it also presents significant toxicological concerns that require careful assessment to ascertain its therapeutic viability. The primary source of these risks is the high concentration of β-carboline alkaloids, which display dose-dependent effects that can range from neuroprotective to neurotoxic, and may negatively interact with drugs that impact the Central Nervous System (CNS).

Therapeutic Window and LDex

The therapeutic window for *Peganum harmala* is quite limited. In rodents, the estimated oral LD_{50} values for harmaline and harmine fall between 30 and 50 mg/kg, varying based on the administration route and species involved.[32,39,119] When administered orally, extracts from *P. harmala* seeds demonstrate an LD_{50} of roughly 2.8 g/kg in mice; however, this value decreases significantly with intraperitoneal administration, underscoring the significance of toxicity being route-dependent.[41,120]

At lower concentrations, β-carbolines function as reversible MAO-A inhibitors exhibiting neuroprotective qualities. Conversely, at elevated doses, these substances can penetrate

Table 1: Key Active Alkaloids in *Peganum harmala* and Their Neuropharmacological Effects.

Alkaloid	Chemical Class	Mechanism of Action	Pharmacological Effect	Reference Numbers
Harmine	β-carboline	Reversible inhibitor of MAO-A, stimulates BDNF, possesses antioxidant properties.	Antidepressant, anxiolytic, neuroprotective.	[8,49,71,85,88]
Harmaline	β-carboline	Modulates EEG activity, interacts with GABA/NMDA receptors, exhibits proconvulsant effects depending on dosage.	Anticonvulsant at lower doses; tremor-inducing at higher doses.	[44,78,89]
Tetrahydroharmine	β-carboline	Enhances serotonergic transmission.	Mild neuromodulatory effects.	[52]
Vasicine	Quinazoline	Acts as a bronchodilator with sedative properties; structurally different from other alkaloids.	Provides non-neurological support and aids in bronchodilation.	[10,53,54]

Table 2: Bioelectrical Effects of *Peganum harmala* on Cortical Activity and EEG Patterns.

Experimental Model	Compound	Observed EEG Effects	Brain Region Involved	Clinical Relevance	Reference Numbers
Rats	Harmaline	Enhanced theta/delta power, spike-wave discharges.	Cortex, thalamus	Absence epilepsy, essential tremor.	[44,89,90,92]
Mice	Harmaline	Paroxysmal discharges, rhythmic tremors.	Inferior olive, cortex	Seizure models, motor tremor.	[89, 94, 95]
Mice	Harmine	Decreased hyperexcitability under stress	Amygdala, hippocampus	Anxiolytic effect, neuroplasticity.	[49, 71]
Cats	Harmaline	Synchronized oscillations in mesencephalic circuits.	Brainstem, cortex	Experimental EEG mapping.	[92]

the blood-brain barrier and provoke CNS excitation along with symptoms such as tremors and seizure-like behavior in experimental models.[38,121]

Neurotoxicity vs. Neuroprotection

The contrasting effects of harmala alkaloids-being neurotoxic at elevated doses yet neuroprotective at lower levels-highlight the necessity for careful dosing and standardization practices. Research indicates that high concentrations of harmaline can lead to oxidative stress, mitochondrial dysfunction, and apoptosis in cortical neurons.[6]

In contrast, when administered at lower doses, both harmine and harmaline can enhance BDNF expression while decreasing lipid peroxidation and maintaining neuronal integrity, suggesting their potential as neuroprotective agents under regulated conditions.[85,88]

This duality underscores the critical importance of strict dosage management when utilizing these compounds in either experimental or clinical environments.

Adverse Effects at High Doses

Adverse reactions associated with high doses of *P. harmala* include:

- Tremors, ataxia, hyperreflexia, and seizures.
- Nausea, vomiting, bradycardia, and hypotension.
- Hallucinations, agitation, and delirium.

There have been cases of human intoxication linked to consuming large amounts of *P. harmala* seeds within traditional medicinal applications. Symptoms typically resemble those associated with serotonergic excesses indicating a toxicity profile similar to MAO inhibitors.[75,121]

One documented case reported status epilepticus and coma following ingestion of approximately 50 g of harmala seeds.[122] While these effects appear reversible with appropriate medical support, they underline the clinical risks involved with unsupervised consumption.

Interaction with CNS-Active Drugs

The β-carboline alkaloids found in *P. harmala* inhibit MAO-A activity responsible for metabolizing serotonin, norepinephrine, and dopamine. Co-administration alongside SSRIs or tricyclic antidepressants or serotonergic psychedelics may provoke serotonin syndrome-a serious condition characterized by hyperthermia along with agitation and neuromuscular disturbances.[123]

Furthermore, *Peganum harmala* may enhance the sedative effects of CNS depressants like benzodiazepines, opioids, and barbiturates through synergistic modulation of GABAergic pathways.[124] Such interactions necessitate heightened caution when combining *P. harmala* with prescribed psychotropic medications.

THERAPEUTIC POTENTIAL AND CLINICAL TRANSLATION

Peganum harmala exhibits a broad pharmacological profile, which includes monoamine oxidase inhibition, modulation of neurotransmitters, regulation of electrophysiological processes, antioxidant properties, and neurotrophic support. This multifaceted action renders it a promising candidate for addressing diverse neuropsychiatric and neurodegenerative disorders.

Possible Use in Depression, Epilepsy, PTSD, and Anxiety

A variety of preclinical studies indicate that *P. harmala* effectively diminishes depressive behaviors, alleviates anxiety symptoms, and reduces seizure occurrences. The primary alkaloid harmine

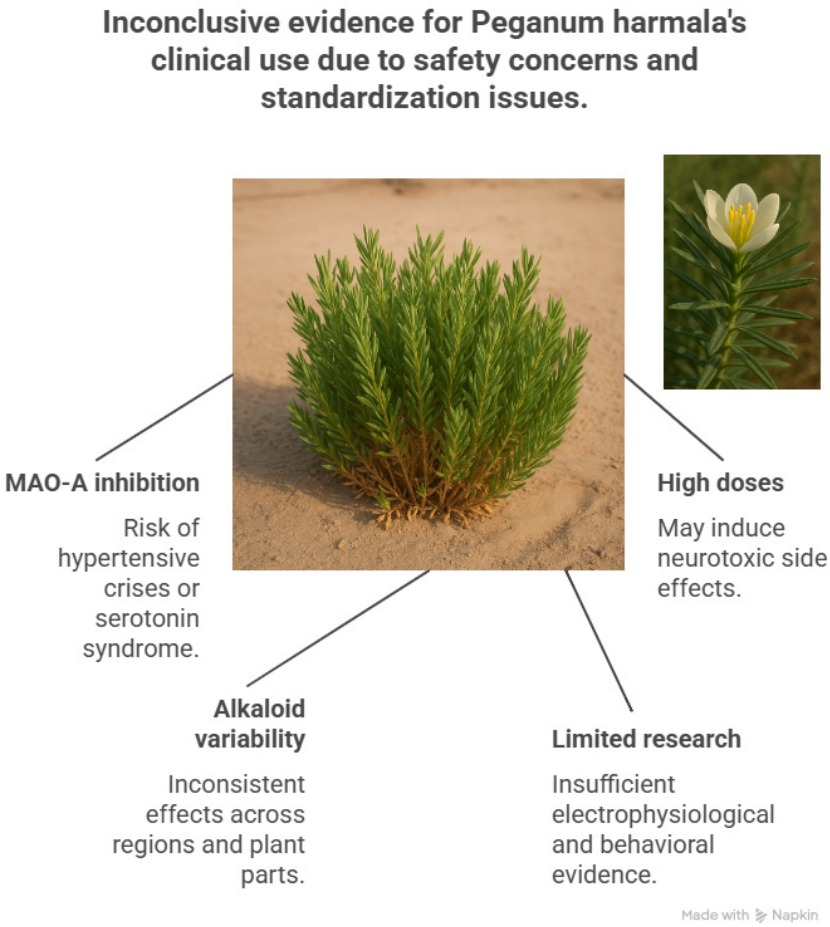

Figure 2: Barriers to the clinical use of *Peganum harmala*.

has demonstrated antidepressant effects that are comparable to those of fluoxetine and imipramine in animal studies.[6,7] The underlying mechanisms involve enhanced serotonin availability, increased BDNF levels, and modulation of the HPA axis.[121,125]

In epilepsy models, harmaline displays both proconvulsant and anticonvulsant properties based on dosage and experimental context, underscoring its intricate interactions with GABAergic and glutamatergic systems.[126] Additionally, harmine has exhibited anxiolytic effects through serotonergic and GABAergic pathways, positioning it as a potential candidate for treating PTSD and stress-related conditions.[69]

Its effect on cortical excitability alongside thalamocortical oscillations further suggests its applicability in managing attention-deficit disorders and essential tremor.[127]

Current Limitations in Translating to Human Use

Despite encouraging results from preclinical investigations, several challenges hinder the clinical application of *P. harmala*-based treatments:

Concerns regarding toxicity arise primarily due to its narrow therapeutic window coupled with MAO-A inhibition-related interactions that present significant safety issues.[9,128]

The absence of standardized extract formulations along with variability in β-carboline concentrations across different regional strains hampers reproducibility efforts.[129]

Currently lacking are large-scale clinical trials that assess the safety or efficacy of *P. harmala* for depression, epilepsy, or anxiety disorders in humans.[36,38]

Moreover, regulatory obstacles surrounding psychoactive substances have historically dampened interest in botanicals rich in β-carbolines.[29] Although the pharmacological mechanisms of *Peganum harmala* have been progressively elucidated, its application in clinical settings has yet to expand significantly. In addition to understanding individual mechanisms, it is essential to identify the broader challenges that account for the slow uptake in clinical practice, despite its promising potential. These challenges encompass regulatory issues, toxicological concerns, biochemical factors, and methodological hurdles that need to be tackled within a cohesive translational approach. For a visual summary of these limitations, see Figure 2.

This illustration highlights four primary obstacles: (1) the potential for serotonergic toxicity and hypertensive crises linked to MAO-A inhibition; (2) neurotoxicity that escalates with dosage, especially at elevated levels; (3) inconsistencies in β-carboline alkaloid concentrations among different parts of the

plant and from various geographical origins; and (4) the absence of standardized extracts coupled with limited electrophysiological studies. Together, these issues hinder its progression towards becoming a safe and regulated therapeutic option targeting the central nervous system.

Potential for Drug Formulation or Standardized Extracts

To address these challenges effectively

Standardized extracts with clearly defined concentrations of harmine and harmaline should be developed.

There is a need to investigate low-dose formulations or semi-synthetic derivatives that possess improved safety profiles.

Designing slow-release or targeted delivery mechanisms could help mitigate CNS-related toxicity risks.

Initial research is underway examining encapsulation techniques and nanoparticle-based delivery systems for *P. harmala* alkaloids to improve bioavailability while minimizing peak plasma toxicity.[130]

This development may pave the way for creating β-carboline-based pharmaceuticals inspired by *P. harmala*.

Interdisciplinary Implications: Phytochemistry, Psychiatry, Electrophysiology

Research on Peganum harmala encompasses multiple disciplines

Phytochemistry provides valuable insights into optimizing methods for extracting alkaloids as well as their purification and structural modification.[131]

Psychiatry paired with behavioral neuroscience establishes a clinical framework to evaluate its anxiolytic and antidepressant potential.[132]

Electrophysiology contributes to understanding its influence on brain oscillations as well as cortical excitability and seizure thresholds.[133]

An interdisciplinary approach integrating these fields may unlock the therapeutic potential of *Peganum harmala* while facilitating its integration into evidence-based neuropharmacology practices. offers a detailed summary of neuropsychiatric and neurological conditions that may benefit from the therapeutic use of *Peganum harmala*. This classification is grounded in mechanistic reasoning obtained from preclinical studies and electrophysiological findings.

RESEARCH GAPS AND FUTURE DIRECTIONS

While there is an expanding collection of preclinical data underscoring the neuropharmacological capabilities of *Peganum harmala*, significant research deficiencies persist that need to be addressed for its safe and effective application in clinical settings.

Need for *in vivo* Synergy Studies with CNS Drugs

So far, most pharmacological studies on *P. harmala* have concentrated on its individual effects. However, due to its MAO-A inhibitory properties and influence on various neurotransmitter systems, it is essential to investigate its synergistic or antagonistic interactions with well-established CNS medications, including:

- Selective Serotonin Reuptake Inhibitors (SSRIs).
- Anticonvulsants (e.g., valproate, carbamazepine).
- Atypical antipsychotics.

Such investigations would clarify additive effects, potential toxicity concerns, and drug interaction profiles, particularly in relation to serotonin syndrome, seizure thresholds, and dopaminergic modulation.[134]

Absence of Clinical Trials

Although animal models have shown antidepressant, anxiolytic, anticonvulsant, and neuroprotective effects of *P. harmala*, there is currently a total lack of rigorously designed clinical trials assessing its efficacy in humans.[135] This limitation significantly hinders its translational relevance.

Future research should focus on:

- Phase I safety trials utilizing standardized low-dose extracts.
- Controlled human studies addressing mild-to-moderate depression, generalized anxiety disorder, or treatment-resistant epilepsy.
- Comparative studies evaluating efficacy against standard pharmaceuticals.

These initiatives would not only substantiate therapeutic claims but also help determine appropriate dosing guidelines and safety profiles.[36]

Need for Bioelectrical Measurement Studies (EEG, MEA)

Much of the current literature concerning the bioelectrical effects of *P. harmala* relies on basic EEG measurements or behavioral outcomes. There is a pressing need for more sophisticated electrophysiological studies such as:

- High-resolution Electroencephalography (EEG) to map cortical oscillatory changes across different frequency bands.
- Multielectrode Array (MEA) systems for real-time analysis of neuronal network activity.
- Optogenetics or calcium imaging techniques to visualize circuit-level dynamics.

These methodologies would enhance understanding of how *P. harmala* affects thalamocortical loops, spike synchrony, and plasticity-particularly relevant for conditions characterized by network hyperexcitability.[136]

Suggestions for Targeted CNS Disorders

Considering its pharmacological properties and bioelectrical profile, *Peganum harmala* could be strategically explored in relation to:

- **Schizophrenia:** due to its dopaminergic, glutamatergic, and neurotrophic actions.[10]
- **Epilepsy:** because of its dual influence on GABAergic and excitatory pathways.[137]
- **Obsessive-Compulsive Disorder (OCD) and PTSD:** through mechanisms related to serotonergic activity and neuroplasticity enhancement.[138]
- **Parkinson's disease:** potentially owing to MAO-B inhibition and antioxidant protection.[15]

These applications necessitate well-designed disease-specific models along with dose-finding studies and longitudinal outcome assessments to thoroughly evaluate benefit-risk ratios.

CONCLUSION

Peganum harmala presents itself as a phytotherapeutic compound with noteworthy neuropharmacological and electrophysiological characteristics that engage various mechanistic pathways associated with Central Nervous System (CNS) disorders. Its β-carboline alkaloids, particularly harmine and harmaline, exhibit reversible inhibition of Monoamine Oxidase-A (MAO-A), promote Brain-Derived Neurotrophic Factor (BDNF) signaling, modulate both GABAergic and glutamatergic systems, and reduce oxidative stress. These effects contribute to the observed neuroprotective, antidepressant, anxiolytic, and anticonvulsant properties in preclinical studies.

Simultaneously, bioelectrical research indicates that harmala can influence cortical excitability, synchronize thalamocortical oscillations, and modify EEG patterns. This suggests it operates through a combined neurochemical and electrophysiological mechanism. Such attributes set *P. harmala* apart from traditional mono-target therapies and highlight its potential as a candidate for holistic neuropsychiatric treatment.

Despite its promise, progress in clinical application is hindered by significant issues: a limited therapeutic index, dose-related neurotoxicity, inconsistent alkaloid concentrations among plant sources, and an absence of human clinical trials. Addressing these obstacles requires comprehensive toxicological assessments, the creation of standardized bioavailable formulations, and phased clinical validation to evaluate safety, efficacy, and possible drug interactions.

In conclusion, while *Peganum harmala* holds considerable pharmacological potential, its practical clinical application is dependent on a thorough and collaborative research approach. Integrating its ethnopharmacological heritage with contemporary neuroscientific study may pave the way for innovative therapeutic options for CNS disorders related to stress, mood regulation, and excitability.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACTH: Adrenocorticotropic Hormone; **ADHD:** Attention-Deficit/Hyperactivity Disorder; **BDNF:** Brain-Derived Neurotrophic Factor; **CNS:** Central Nervous System; **CRH:** Corticotropin-Releasing Hormone; **DA:** Dopamine; **EEG:** Electroencephalography; **FST:** Forced Swim Test; **GABA:** Gamma-Aminobutyric Acid; **HPA:** Hypothalamic–Pituitary–Adrenal (Axis); **LD_{50}:** Median Lethal Dose; **MAO-A:** Monoamine Oxidase A; **MEA:** Multielectrode Array; **NE:** Norepinephrine; **NMDA:** N-Methyl-D-Aspartate; **OCD:** Obsessive–Compulsive Disorder; **PFC:** Prefrontal Cortex; **PTSD:** Post-Traumatic Stress Disorder; **ROS:** Reactive Oxygen Species; **SSRI:** Selective Serotonin Reuptake Inhibitor; **TST:** Tail Suspension Test.

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