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Review Article

Synergistic Neuropsychopharmacological Potential of *Peganum harmala* and *Cucurbita pepo*: A Narrative Review of Mechanisms, Evidence, and Toxicological Cautions

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ABSTRACT

Neuropsychiatric conditions, including depression and anxiety, pose significant challenges to global health. These issues are often intensified by the limitations of existing pharmacological treatments, which may have delayed effects, incomplete responses, and various side effects. Consequently, there is a growing interest in herbal therapies that provide diverse neuropharmacological benefits. This narrative review aims to critically analyze the potential synergistic interaction between *Peganum harmala* and *Cucurbita pepo* in influencing neurobiological pathways associated with mood disorders, drawing on current phytochemical, pharmacological, and preclinical research. A comprehensive literature review was conducted utilizing PubMed, Scopus, and Google Scholar to identify studies-both *in vitro* and *in vivo*-as well as mechanistic investigations related to *P. harmala* and *C. pepo*. The emphasis was placed on serotonergic modulation, antioxidant effects, GABAergic regulation, and mitochondrial support. *P. harmala* is known to contain β-carboline alkaloids (such as harmine and harmaline) that inhibit MAO-A enzymes, thereby increasing monoamine levels and modulating GABA-A receptors. On the other hand, *C. pepo* contributes tryptophan, magnesium, and antioxidants that aid serotonin production and offer neuroprotective benefits. While both substances demonstrate antidepressant- and anxiolytic-like effects individually in animal models, their combined use has not yet been investigated. Concerns about toxicity primarily relate to *P. harmala's* potential neurotoxicity and interactions with serotonergic systems; however, *C. pepo* is generally regarded as safe with a substantial safety margin. Although theoretical synergy exists based on mechanistic evidence, direct empirical validation is currently lacking. The suggested combination of *Peganum harmala* and *Cucurbita pepo* presents an intriguing multi-target approach for mood management. Nonetheless, the lack of clinical trials, data on *in vivo* synergy, and assessments of human safety restricts immediate application of this strategy. Future research should emphasize experimental validation along with toxicological modeling and AI-assisted formulation techniques to advance this promising phytotherapeutic idea into practical clinical use.

Keywords: *Peganum harmala*, *Cucurbita pepo*, β-carbolines, MAO-A Inhibition, Tryptophan, Phytotherapy, Neuropsychiatric Disorders, Depression, Anxiety, Antioxidant, GABAergic Modulation, Serotonin, Herbal synergy, Neuroprotection.

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INTRODUCTION

Mental health disorders, including depression and anxiety, are among the primary contributors to global disability, impacting more than 970 million individuals globally and significantly affecting both premature death rates and overall quality of life.[1-4] The World Health Organization (WHO) reports that depressive disorders impact over 280 million people, with a rising incidence noted in low- and middle-income nations.[5-7] These mental health issues also create significant socioeconomic challenges due to decreased productivity, escalating healthcare expenses, and societal stigma.[8,9] Even with the presence of pharmacological treatments-particularly Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)-results remain unsatisfactory for a considerable number of patients.[10-13] Antidepressants typically require 4 to 6 weeks to produce noticeable effects, with approximately 30% to 50% of patients experiencing either partial or no response to first-line therapies.[14,15] Furthermore, adverse effects such as sexual dysfunction, weight gain, and emotional numbness frequently hinder treatment adherence.[16] Notably, Treatment-Resistant Depression (TRD) impacts around one-third of affected individuals, highlighting the pressing need for innovative

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multimodal approaches that are both effective and accessible.[17-19] In light of this situation, there has been a surge in interest regarding phytomedicine-the application of plant-based therapies-as either primary or supplementary treatments within psychiatric care.[20,21] Phytochemicals are gaining recognition for their ability to act on multiple targets through mechanisms such as neurotransmitter modulation, antioxidant properties, anti-inflammatory actions, and neuroprotective effects.[22-24] Among the medicinal plants gaining renewed focus are *Peganum harmala* (Syrian rue) and *Cucurbita pepo* (pumpkin). *Peganum harmala* is abundant in β-carboline alkaloids like harmine and harmaline that function as reversible Monoamine Oxidase-A (MAO-A) inhibitors.[25,26] These compounds can increase levels of serotonin, dopamine, and norepinephrine within the brain-mirroring some effects seen with specific antidepressants-and demonstrate potential efficacy in preclinical studies involving depression and anxiety.[27-29] Nevertheless, concerns about its limited therapeutic range and potential neurotoxicity necessitate thorough toxicological assessments.[30,31] Conversely, *Cucurbita pepo* is not generally categorized as psychoactive but possesses nutritional elements that may hold significance for mental wellness. This includes tryptophan-a precursor for serotonin-alongside magnesium, zinc, and carotenoids that have been linked to mood stabilization and neurocognitive protection.[32-36] Epidemiological data indicate an inverse relationship between diets high in magnesium or tryptophan and depressive symptoms; additionally dietary supplementation with pumpkin seeds has exhibited anxiolytic and antidepressant benefits in animal research.[37-39] Considering their unique yet complementary neuropharmacological characteristics-where *P. harmala* increases monoamine availability while *C. pepo* supplies precursors and cofactors necessary for neurotransmitter production-it is logical to investigate their combined effect on mood-related pathways. Thus, this narrative review aims to thoroughly assess the current evidence regarding the neuropsychiatric implications of *Peganum harmala* and *Cucurbita pepo*. It will also explore their mechanistic interactions while outlining future avenues for preclinical validation along with safe clinical application.

Botanical and Phytochemical Overview

Peganum harmala

Peganum harmala L., referred to as Syrian rue, is a perennial herbaceous plant from the *Zygophyllaceae* family, indigenous to the Mediterranean area, Central Asia, and segments of the Middle East.[40-44] This plant has been traditionally utilized for various applications, including spiritual ceremonies, antimicrobial fumigation, and as a folk remedy for ailments such as depression, epilepsy, insomnia, and inflammation.[45,46] Within Unani and Iranian traditional medicine, it is frequently characterized as a nervine tonic and sedative specifically aimed at addressing "melancholic states".[46-48] In terms of its phytochemical profile, *P. harmala* is distinguished by its considerable levels of β-carboline alkaloids-most notably harmine, harmaline, and harmalol-primarily found in the seeds with lower concentrations in the roots and stems.[49-51] These compounds are associated with a variety of biological effects including antioxidant activity, antitumor properties, antimicrobial effects, and neuropharmacological actions.[52-54] Harmine and harmaline are structurally akin indole alkaloids that strongly bind to Monoamine Oxidase A (MAO-A), functioning as reversible inhibitors of this enzyme.[55-58] By inhibiting MAO-A activity, both harmine and harmaline raise synaptic concentrations of serotonin, dopamine, and norepinephrine-a mechanism similar to that employed by several classes of antidepressants.[59-62] Importantly, unlike irreversible MAO inhibitors such as phenelzine, the reversible nature of harmine's inhibition presents a potentially safer pharmacological profile; however, caution remains necessary.[63-65] Crucially, both harmine and harmaline are lipophilic with low molecular weights (~212 Da), demonstrating efficiency in crossing the Blood-Brain Barrier (BBB) in studies involving rodents as well as computational pharmacokinetic models.[60,66-69] This characteristic enhances their significance for interventions targeting the Central Nervous System (CNS). Furthermore, research indicates that harmine can inhibit efflux transporters like P-Glycoprotein (P-gp), which may further facilitate CNS penetration of concurrently administered medications.[70-72]

Cucurbita pepo

Cucurbita pepo L., known commonly as pumpkin, belongs to the Cucurbitaceae family and is widely cultivated across the globe for its edible fruits and seeds. While primarily enjoyed as a dietary vegetable, *C. pepo* has attracted scientific interest due to its nutritional richness and potential roles in psychotropic support-particularly concerning mood regulation and cognitive health.[73-76] Both the seeds and pulp of *C. pepo* are abundant in various bioactive compounds. Tryptophan-an essential amino acid-is plentiful in pumpkin seeds; it acts as a precursor for serotonin production within the central nervous system.[77,78] Serotonin serves as an important neurotransmitter influencing mood stability, sleep patterns, and emotional processing; thus availability of tryptophan is crucial for its synthesis in the brain.[79-82] Additionally, *C. pepo* provides significant quantities of magnesium, s zinc, and polyunsaturated fatty acids-all vital for neurological function-and has been correlated with reduced risks of depression and anxiety in both epidemiological surveys and intervention studies.[83-87] Notably, magnesium modulates NMDA receptors along with GABAergic signaling, resulting in anxiolytic effects along with antidepressant-like responses.[88,89] Moreover, *C. pepo* contains an array of carotenoids such as beta-carotene, lutein, and zeaxanthin-which are powerful antioxidants recognized for their ability to mitigate oxidative stress alongside neuroinflammation-both elevated conditions present among individuals suffering from mood disorders.[90,91] Antioxidants serve protective functions against hippocampal atrophy along

with dysregulation within HPA axis-characteristic features associated with major depressive episodes.[92,93] The synergistic presence of serotonergic precursors, neuromodulatory minerals, and antioxidant phytochemicals positions *C. pepo* as a promising nutritional element worthy of consideration within diet-based adjunct strategies aimed at enhancing mental health.

Neuropharmacological Properties

Peganum harmala

The neuropharmacological effects of *Peganum harmala* are mainly due to its substantial presence of β-carboline alkaloids, specifically harmine, harmaline, and tetrahydroharmine. These compounds serve as powerful and reversible inhibitors of Monoamine Oxidase-A (MAO-A), an enzyme that breaks down important neurotransmitters like serotonin, dopamine, and norepinephrine.[94-97] By inhibiting MAO-A, harmine and harmaline effectively enhance the synaptic levels of these monoamines, thereby replicating or amplifying the pharmacodynamics associated with conventional antidepressants.[56,98-100] Beyond their influence on monoamine systems, β-carbolines also affect GABAergic neurotransmission. For example, harmaline has been found to interact with GABA-A receptor sites, which enhances inhibitory synaptic activity and contributes to anxiolytic and sedative-like effects.[101-105] This dual action on both monoaminergic and GABAergic systems supports the traditional application of *P. harmala* in addressing neuropsychiatric issues such as anxiety and insomnia.[106, 107] The antidepressant-like effects of *P. harmala* and its alkaloids have been verified through various animal studies, particularly using tests like the Forced Swim Test (FST) and Tail Suspension Test (TST). Harmine significantly decreases immobility time in rodents-a behavioral indicator of antidepressant efficacy-comparable to the impacts seen with imipramine or fluoxetine.[95,96,108] Additionally, chronic administration of harmine has been shown to elevate Brain-Derived Neurotrophic Factor (BDNF) expression in the hippocampus, which is crucial for neuroplasticity and resilience in models of depression.[109,110] However, despite these therapeutic benefits, *P. harmala* raises significant safety concerns. Its β-carboline alkaloids may lead to neurotoxicity, especially when administered at high doses or with prolonged use. Reports from cases and toxicological investigations have highlighted adverse effects such as hallucinations, tremors, seizures, and in severe instances, coma.[56, 111-113] These side effects are likely a result of MAO-A inhibition leading to serotonin syndrome-particularly when combined with serotonergic medications or tyramine-rich foods.[113-115] Moreover, because harmine interacts with several central nervous system targets, there is an increased risk for off-target excitotoxicity and hepatotoxicity if not used judiciously.[116,117] Consequently, while *P. harmala* demonstrates notable neuropharmacological activity, it necessitates careful dose regulation along with thorough toxicological assessment and screening for contraindications prior to any clinical implementation.

Cucurbita pepo

In contrast to *Peganum harmala, Cucurbita pepo* does not function through direct neurotransmitter inhibition but instead offers nutritional support essential for synthesizing neurotransmitters like serotonin. The seeds are abundant in L-tryptophan-the necessary amino acid precursor for serotonin-and its bioavailability is critical for producing central serotonin levels during periods of psychological stress or dietary deficit.[73,74] Increased peripheral tryptophan concentrations have been linked to better mood regulation, improved sleep patterns, and decreased aggression based on both human and animal studies.[80,118] Alongside tryptophan content, *C. pepo* is rich in antioxidants such as vitamin E and β-carotene among other carotenoids that help mitigate oxidative stress-a recognized contributor to major depressive disorders and anxiety conditions.[39,73,74,119,120] Elevated levels of Reactive Oxygen Species (ROS) within the brain can disrupt mitochondrial function as well as synaptic plasticity-factors that contribute to neurodegeneration and mood disturbances.[77,121] The antioxidant properties found in pumpkin extracts have shown protective effects against chronic stress-induced damage in rodent models exposed to neurotoxins.[75,122,123] Another vital element present in pumpkin seeds is magnesium which plays a crucial role in regulating NMDA receptors while maintaining balance within glutamatergic pathways-essential processes for stabilizing neuropsychiatric health.[124-127] Deficits in magnesium have been strongly linked with heightened excitotoxicity alongside neuronal hyperexcitability leading to depressive symptoms; supplementation has demonstrated positive outcomes regarding mood enhancement during clinical trials.[128-130] Research involving human subjects regarding pumpkin seed usage within psychiatric contexts remains limited yet promising. A small pilot study indicated that supplementation with pumpkin seed oil led to diminished anxiety symptoms among children.[131,132] Moreover, observational research suggests that higher dietary intake levels of magnesium alongside tryptophan and zinc-all components found in *C. pepo*-are correlated with reduced rates of depression across population samples.[35,133] In summary, while *Cucurbita pepo* may not function explicitly as a psychoactive substance itself; its nutrient-driven influence on serotonergic pathways along with antioxidant properties positions it as a potentially beneficial adjunct for mood management along with overall neuropsychiatric support.

Mechanistic Rationale for Synergy

The potential synergistic interaction between*Peganum harmala* and *Cucurbita pepo* is rooted in their complementary mechanisms, which affect critical neurobiological systems implicated in mood disorders. These include enhancement of serotonergic activity, antioxidant and anti-inflammatory effects,

modulation of GABAergic transmission, and stabilization of mitochondrial function-factors increasingly acknowledged in psychoneuroimmunology models concerning depression and anxiety.[134,135]

Convergence on Serotonergic Pathways

A key area of mechanistic overlap is the enhancement of serotonergic neurotransmission through two synergistic pathways

- *P. harmala* provides reversible MAO-A inhibition via β-carboline alkaloids (such as harmine and harmaline), preventing serotonin degradation and thus increasing its synaptic availability.[53,94,136]
- Concurrently, *C. pepo* offers L-tryptophan, which is the rate-limiting precursor for serotonin synthesis, thereby boosting its endogenous production.[94,137,138]

This dual mechanism-enhancing synthesis through tryptophan while inhibiting breakdown via MAO-A-creates a pharmacodynamic synergy that could enhance serotonergic tone more effectively than either compound alone.[50,95,139] Improved serotonergic activity has been linked to mood regulation, sleep patterns, appetite control, and cognitive functions; disruptions in serotonin signaling are central to the pathophysiology of Major Depressive Disorder (MDD).[140-142] Therefore, the combined effects of *P. harmala* and *C. pepo* may provide comprehensive serotonergic modulation pertinent to neuropsychiatric outcomes.

Antioxidant and Anti-inflammatory Overlap

Both *P. harmala* and *C. pepo* exhibit strong antioxidant properties but through different phytochemical mechanisms. The antioxidant effects of *P. harmala* arise from β-carboline alkaloids that decrease lipid peroxidation and nitric oxide overproduction; meanwhile, *C. pepo* contributes carotenoids (e.g., β-carotene, lutein) along with vitamin E that scavenge Reactive Oxygen Species (ROS) and stabilize neuronal membranes.[143-145] Oxidative stress and inflammation are significantly linked to the development and advancement of psychiatric conditions. Elevated concentrations of pro-inflammatory cytokines, including IL-6, TNF-α, and CRP, have been correlated with the severity of depression and a lack of response to treatment. Approaches that utilize antioxidants have demonstrated potential in mitigating neuroinflammatory effects and improving mood.[146-148] Thus, the convergent antioxidant properties of these two agents may create a neuroprotective synergy particularly relevant for stress-related conditions where glial activation and oxidative damage are significant factors.[149-152]

GABAergic Balance and Mitochondrial Modulation

While *P. harmala* engages directly with GABAergic systems through allosteric modulation of GABA-A receptors, *C. pepo* indirectly supports GABA synthesis due to its magnesium content-a crucial cofactor for Glutamic Acid Decarboxylase (GAD), the enzyme responsible for producing GABA.[153,154]

Impairment in GABAergic inhibition is a known factor contributing to anxiety disorders, insomnia, and emotional instability; thus restoring GABA levels remains a primary objective for many anxiolytic and antidepressant treatments.[155-157] Combining a direct modulator of GABA receptors (*P. harmala*) with an agent that enhances cofactor availability (*C. pepo*) establishes a logical synergistic approach aimed at reducing neural hyperactivity while stabilizing emotional responses. Moreover, mitochondrial dysfunction is recognized as a contributing factor in both mood disorders as well as neurodegenerative diseases. Harmine has demonstrated benefits for mitochondrial bioenergetics by influencing mitochondrial membrane potential and ATP production; extracts from antioxidant-rich *C. pepo* help mitigate mitochondrial oxidative damage while supporting neuronal energy metabolism.[158] These actions can converge to restore cellular equilibrium, diminish neurotoxicity risks, and foster neuroplasticity under chronic stress or depressive conditions.

Synergistic Models in Psychoneuroimmunology

Contemporary understandings of depression and anxiety increasingly utilize psychoneuroimmunology frameworks that emphasize the intricate relationships among immune responses, endocrine stress mechanisms, and central nervous system pathways.[159,160] Elements such as Hypothalamic-Pituitary-Adrenal (HPA) axis dynamics along with microglial activation contribute significantly to neuro progression as well as treatment resistance.[161,162] These pathways, when addressed concurrently, have the potential to produce synergistic effects in influencing neurotransmission, lowering oxidative stress, and diminishing neuroinflammation (Figure 1).

Incorporating

- The impacts of *P. harmala* on monoaminergic systems alongside its influence on GABA,
- The nutritional contributions from *C. pepo*, enhancing both antioxidants' roles alongside serotonin biosynthesis,

This formulation potentially addresses multiple targets within psychoneuroimmunological contexts-suggesting it may be a viable candidate for future multimodal intervention studies.[163,164]

This multi-target convergence offers a compelling rationale for further exploratory research into their combined application in treating neuropsychiatric disorders. To effectively summarize the neurobiological mechanisms and their suggested interplay, Table 1 presents a methodical comparison of *Peganum harmala* and *Cucurbita pepo* in relation to essential pharmacological areas.

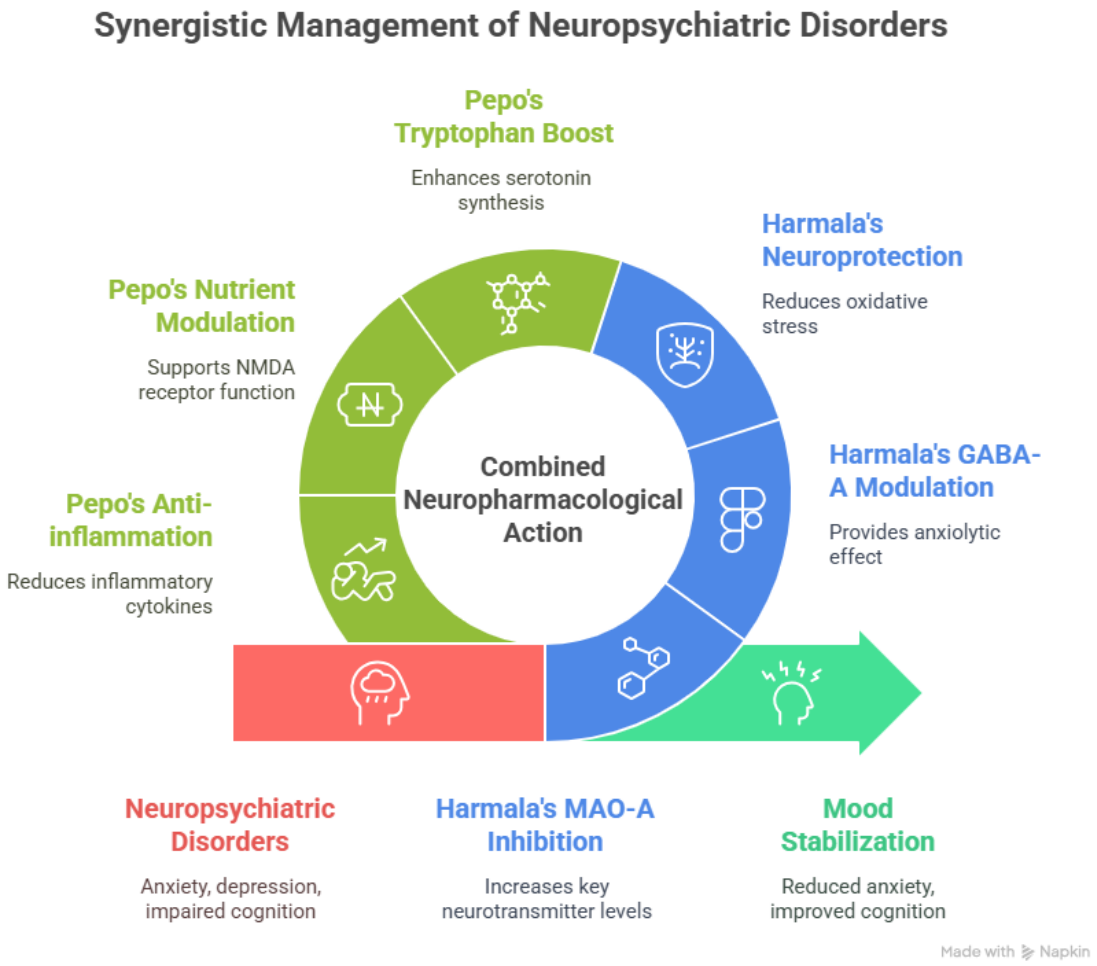

Figure 1: The combined neuropharmacological effects of *Peganum harmala* and *Cucurbita pepo* contribute to mood stabilization and enhanced cognitive function through mechanisms involving monoamine modulation, anti-inflammatory properties, antioxidant activity, and GABAergic pathways.

Preclinical Evidence

The increasing interest in the ethnopharmacological properties of *Peganum harmala* and *Cucurbita pepo* has not yet led to extensive preclinical research on their individual or combined neuropsychiatric effects, although the existing studies are encouraging. Evidence from animal models, cellular assays, and initial pharmacokinetic evaluations supports their potential as psychotropic agents. Nonetheless, significant data deficiencies-especially concerning their synergistic effects-limit the ability to draw translational conclusions. A comprehensive overview of the existing preclinical research highlighting the neuropsychiatric possibilities of *Peganum harmala* and *Cucurbita pepo* can be found in Table 2.

Animal Studies: Depression and Anxiety Models

The primary β-carbolines found in *P. harmala*, namely harmine and harmaline, have shown considerable antidepressant-like properties in mouse models. In validated behavioral tests for depression such as the Forced Swim Test (FST) and Tail Suspension Test (TST), harmine significantly decreased immobility times in a dose-dependent manner, showing results similar to those of fluoxetine and imipramine.[165-168] Repeated administration of harmine has also been associated with an increase in hippocampal BDNF expression, which is crucial for neuroplasticity and the efficacy of antidepressants.[169-171] Furthermore, harmaline has demonstrated anxiolytic effects during open field tests and Elevated Plus Maze (EPM) assessments, likely through modulation of GABA-A receptors and inhibition of central MAO-A activity.[166,168,172] The β-carbolines have also been noted to alleviate stress-related cognitive decline and inhibit hyperactivity of the HPA axis, both factors involved in the development of depression.[173,174] For *Cucurbita pepo*, though there are fewer studies available, some research suggests its anxiolytic and antidepressant-like effects may arise from its content of tryptophan, magnesium, and antioxidants. In murine studies, pumpkin seed extract was found to significantly lessen anxiety behaviors observed in light-dark box tests and EPMs while

Table 1: Synergistic Neuropsychopharmacological Actions of *Peganum harmala* and *Cucurbita pepo*.

Pharmacological Target	*Peganum harmala* (PH) Action	*Cucurbita pepo* (CP) Action	Proposed Synergistic Benefit
Monoamine Modulation	β-carbolines (harmine, harmaline) inhibit MAO-A, increasing serotonin and dopamine.[94,136]	-	Enhanced monoamine levels through MAO-A inhibition combined with precursor availability.[94,137-139]
Serotonergic Synthesis and Availability	Prevents degradation of 5-HT indirectly.[53,94]	Tryptophan acts as a precursor for the biosynthesis of 5-HT.[94,137,138]	Boosting serotonin through dual pathways: synthesis enhancement and degradation prevention.
GABAergic Enhancement	Harmaline influences GABA-A receptors to produce anxiolytic effects.[101-105]	Magnesium supports GABA synthesis by acting as a cofactor for GAD.[153,154]	GABAergic enhancement achieved directly by PH and via cofactors from CP.
Antioxidant Defense	Lowers lipid peroxidation and oxidative stress levels.[143-145]	Carotenoids (β-carotene, lutein) along with vitamin E diminish ROS levels.[143-145]	Comprehensive reduction of oxidative stress due to both plant properties.
Neuroinflammation	Reduces pro-inflammatory cytokines such as IL-6 and TNF-α.[145-147]	Suppresses the release of nitric oxide and inflammatory cytokines.[146-148]	Strengthened anti-inflammatory effects potentially reducing neuroimmune activation.
Mitochondrial Support	Enhances mitochondrial membrane potential and ATP production.[158]	Shields mitochondria from oxidative damage.[158]	Combined protective mechanisms improve neuronal energy balance.
Neuroplasticity (BDNF)	Increases BDNF levels in the hippocampus of rodents.[109,110]	May play a role in enhancing mood resilience and cognitive function.[73-75]	Improved plasticity and mood recovery through BDNF modulation alongside serotonergic support.
Blood-Brain Barrier Penetration	Lipophilic β-carbolines (~212 Da) effectively cross the Blood-Brain Barrier (BBB)[60,66-69]	Lipophilic antioxidants may also aid in central nervous system access.[191]	Collaborative mechanisms enhance CNS penetration and overall bioavailability.

also reducing immobility time in FSTs.[73,74,76] These outcomes were linked to increased serotonin levels within the brain along with heightened activity of antioxidant enzymes.[78,175] Notably, no published research has explored the combined administration of *P. harmala* and *C. pepo* within any neurobehavioral study framework-a critical gap in current knowledge.

Cell-Based Studies

In vitro investigations have revealed that harmine along with related alkaloids can:

- Inhibit Monoamine Oxidase-A (MAO-A) activity at nanomolar concentrations within human cell lines.[96,176,177]
- Decrease oxidative stress indicators (such as malondialdehyde and reactive oxygen species) in neuronal cultures.[178,179]
- Encourage neuronal differentiation as well as dendritic branching in PC12 cells, indicating a role in neurogenesis and synaptic plasticity.[180,181]

Additionally, harmine has been shown to influence Wnt/β-catenin signaling pathways that are gaining recognition for their involvement in mood disorder etiology and responses to antidepressants.[182]

On the other hand, extracts from *Cucurbita pepo*, especially its oil and hydroalcoholic forms have exhibited:

- Neuroprotective qualities against cytotoxicity induced by Hydrogen peroxide (H_2O_2) in SH-SY5Y neuroblastoma cells.[183]
- A decrease in nitric oxide production alongside reduced pro-inflammatory cytokine release when microglial cells were stimulated by Lipopolysaccharides (LPS).[184]
- An increase in cellular glutathione levels which enhances its antioxidant function.[185]

Once more, there have been no reported co-culture or dual-extract experiments involving both *P. harmala* and *C. pepo* aimed at examining synergistic effects on cytoprotection or pathways related to neuroinflammation or serotonin synthesis.

Table 2: Preclinical Evidence Indicating the Neuropsychiatric Potential of *Peganum harmala* and *Cucurbita pepo*.

Study Type/Model	Agent	Key Outcome	References
Forced Swim Test (FST), Tail Suspension Test (TST)	Harmine (*P. harmala*)	Decreased immobility time; increased BDNF expression in the hippocampus.	[165-171]
Elevated Plus Maze (EPM), Open Field Test	Harmaline (*P. harmala*)	Reduced anxiety behaviors through GABAergic modulation.	[172]
Chronic Unpredictable Mild Stress (CUMS) Model	Harmine (*P. harmala*)	Decreased depressive behaviors; modulation of monoamines and HPA axis.	[173,174]
SH-SY5Y Cell Line (Oxidative Stress Model)	*C. pepo* seed oil	Increased glutathione levels; decreased ROS production.	[183-185]
PC12 Cell Line (Neurogenesis and Differentiation)	Harmine (*P. harmala*)	Enhanced neurodifferentiation and dendritic branching.	[180,181]
LPS-Stimulated Microglia (Inflammation Model)	*C. pepo* extract	Decreased NO production; reduced cytokines (IL-6, TNF-α).	[184]
H_2O_2-Induced Cytotoxicity (Neuroprotection Model)	Harmine (*P. harmala*)	Lowered oxidative stress markers (MDA, ROS).	[178,179]
Rodent Cognitive Tests (Memory and Learning)	*C. pepo* extract	Enhanced spatial memory and decreased anxiety levels.	[73-75]
Adrenal Gland Inflammatory Marker Expression	*C. pepo* seed extract	Reduction of IL-1β, IL-6, TNF-α in adrenal tissue samples.	[74]
P-glycoprotein Modulation at Blood-Brain Barrier	Harmine (*P. harmala*)	Inhibition of P-glycoprotein; increased CNS penetration of neuroactive agents.	[189,190]

Pharmacokinetics and Blood-Brain Barrier (BBB) Penetration

Pharmacokinetic analyses indicate that both harmine and harmaline possess advantageous lipophilicity along with low molecular weights (~212 Da), allowing for effective penetration through the BBB via passive diffusion.[60,66,186,187] Within rodent models, peak concentrations of harmine occur between 30-60 min following intraperitoneal injection-aligning with observed central behavioral impacts.[188] Moreover, harmine is known to inhibit P-Glycoprotein (P-gp), a key efflux transporter at the BBB; this could potentially enhance not only its own availability but also that of co-administered compounds within the Central Nervous System (CNS).[189,190] This characteristic raises possibilities for pharmacokinetic synergy when used alongside other neuroactive substances. Conversely, *C. pepo* has not been comprehensively studied regarding its pharmacokinetics related to central bioavailability. Although certain lipophilic components such as carotenoids or fatty acids may be able to cross into the CNS barrier; specific investigations examining how active constituents like tryptophan or magnesium behave when delivered as a whole extract remain absent.[191]

Data Gaps

Despite promising evidence surrounding each substance independently; several critical data gaps continue to exist:

- A lack of animal studies assessing simultaneous administration of both*P. harmala* and*C. pepo.*
- Absence of dose-response synergy investigations focusing on behavior modification or oxidative stress.
- No pharmacokinetic/pharmacodynamic interaction studies available that could establish safety margins or metabolic interferences.
- The lack of validated computational models for synergy or docking studies concerning combined bioactive compounds.

Consequently, while data regarding monotherapy shows promise; hypotheses surrounding synergistic benefits remain theoretical necessitating further mechanistic exploration along with toxicological assessments for translation into practical applications.

Toxicology and Drug Interaction Considerations

The neuropharmacological potential of *Peganum harmala* and *Cucurbita pepo* requires careful evaluation of their associated toxicological hazards and likelihood of drug interactions, especially in the context of neuropsychiatric uses. While *C. pepo* is largely considered safe, *P. harmala* has a restricted therapeutic range, with its β-carboline alkaloids exhibiting neuroactivity, hepatotoxicity, and the potential to cause severe pharmacodynamic interactions.

Peganum harmala: Toxicity Data

The seeds of *P. harmala* contain significant amounts of harmaline, harmine, and various other β-carbolines that reveal a toxicity profile dependent on dosage. Acute toxicity assessments in rodent models have indicated an oral LD_{50} ranging from approximately 300-500 mg/kg for harmaline and 400-600 mg/kg for crude extracts of *P. harmala* seeds.[114,192] At elevated doses, adverse effects such as tremors, convulsions, hyperreflexia, and seizures have been observed, indicative of central nervous system overstimulation.[111,112,193,194] Long-term exposure studies have shown hepatotoxic outcomes marked by elevated liver enzymes, histopathological damage, and oxidative stress within hepatic tissues.[138] These negative effects are intensified by the lipophilicity and accumulation properties of β-carbolines in tissues like the brain and liver over time.[195] In humans, instances of *P. harmala* poisoning are well-documented in ethnomedicinal contexts. Typical symptoms include nausea, vomiting, confusion, hallucinations, agitation, and in severe cases reversible coma.[56,138,196] Symptoms typically manifest within hours post-ingestion and often resolve within several days with appropriate supportive treatment; however, fatalities have been reported following excessive consumption of the seeds or extracts-particularly when combined with alcohol or serotonergic substances.[112,114]

MAO-A Interactions: SSRIs, TCAs, and Tyramine Crisis

Harmine acts as a reversible MAO-A inhibitor (RIMA) and can present significant risks when used alongside serotonin-enhancing drugs such as:

- SSRIs (e.g., fluoxetine or sertraline),
- SNRIs (e.g., venlafaxine),
- Tricyclic Antidepressants (TCAs) (e.g., amitriptyline),
- MAO-B inhibitors,
- Serotonin precursors like L-tryptophan or 5-HTP.

These combinations may trigger serotonin syndrome-a potentially life-threatening condition characterized by autonomic instability alongside neuromuscular issues and altered mental states.[197,198] Although *P. harmala* alkaloids are reversible and selective inhibitors compared to classical MAOIs in terms of interaction profile-which necessitates equal caution.[199] Moreover, inhibition of MAO-A leads to reduced breakdown of tyramine found in aged cheeses, red wines, and certain fermented foods. Increased levels of tyramine can cause hypertensive crises marked by headaches or chest pain along with significantly raised blood pressure.[200-204] While RIMAs like harmine pose a lower risk than irreversible inhibitors (such as phenelzine), dietary precautions are still recommended when they exceed specific thresholds.[205]

Cucurbita pepo: Safety Profile

Conversely, *C. pepo* boasts an extensive safety history as both food source and traditional remedy. Its seeds and oil are widely consumed without notable toxicity-even at high dosages according to research findings.[206,207] Acute toxicity evaluations involving rats or mice have shown no substantial changes regarding body weight or functions related to liver/kidney health at doses up to 2000 mg/kg/day.[208] Rare instances of allergic reactions or contact dermatitis may occur among sensitive individuals due to handling fresh pumpkin pulp or seeds.[209] Critically important is that there is no evidence linking *C. pepo* to neurotoxicity or hepatotoxicity; thus affirming its suitability for dietary supplementation purposes.[80] Nonetheless when combined with MAO inhibitors (such as those derived from *P. harmala*), theoretical concerns arise about possible additive serotonergic effects owing to *C. pepo's* tryptophan content; although no documented cases exist indicating serotonin syndrome from this combination-caution remains prudent particularly within clinical environments or concurrent SSRI usage scenarios.[210] A detailed comparative overview of the toxicological and safety profiles can be found in Table 3.

Research Gaps and Future Directions

Although *Peganum harmala* and *Cucurbita pepo* each show promising neuropharmacological and psychotropic characteristics, there is a notable lack of clinical trials or translational research investigating their combined application in psychiatric disorders. This gap presents a significant opportunity for further exploration, especially considering the potential for a synergistic relationship between these two substances. Numerous preclinical investigations have demonstrated *P. harmala's* modulation of monoaminergic and GABAergic systems through β-carbolines,[211] as well as the contributions of *C. pepo* to serotonin production, antioxidative processes, and NMDA receptor modulation.[50] However, no studies have yet examined their co-administration or assessed interactive safety and effectiveness in either *in vitro* or *in vivo* settings.

In vivo Synergy Studies

There is an immediate need to investigate the combined pharmacodynamic effects and behavioral responses of *P. harmala* and *C. pepo* using established rodent models for depression and anxiety such as:

- Forced Swim Test (FST),
- Tail Suspension Test (TST),
- Elevated Plus Maze (EPM),
- Chronic Mild Stress (CMS).

These experimental models will help evaluate any additive or supra-additive impacts on immobility duration, anxiety levels,

Table 3: Comparative Analysis of Safety and Toxicology for *Peganum harmala* and *Cucurbita pepo*.

Toxicological Parameter	*Peganum harmala* (PH)	*Cucurbita pepo* (CP)
LD_{50} (Oral, Rodents)	Harmaline: 300-500 mg/kg; crude extract: ~400-600 mg/kg.[114,192]	>2000 mg/kg (no acute toxicity signs in rats/mice).[208]
Neurotoxicity Risk	High doses may cause hallucinations, seizures, and coma.[111-113]	No reported neurotoxic effects.[80]
Hepatotoxicity	Increased liver enzymes and histopathological damage in animal studies.[138]	No hepatotoxic effects noted even at high doses.[206,207]
Serotonin Syndrome Potential	Significant risk; contraindicated with SSRIs, TCAs, MAOIs.[197-199]	Minimal risk; theoretical involvement via tryptophan without evidence of syndrome.[210]
MAO-A Interaction Risk	Strong reversible inhibition of MAO-A by β-carbolines.[94,136]	No direct MAO inhibition; tryptophan precursor might enhance effects.[94,137]
Dietary Safety Classification	Not classified as GRAS; usage is restricted in clinical settings.[111]	Generally Recognized as Safe (GRAS) for food and supplements.[206]
Clinical Case Reports	Multiple poisoning incidents linked to traditional use documented.[56,138,196]	No known cases of clinical toxicity from consumption.[80]
Drug-Drug Interaction (SSRIs, TCAs)	Documented risk of serotonin syndrome in human cases.[113-115]	No adverse interactions reported with antidepressants.[210]
Allergenicity	Rare instances of non-specific reactions; not typically allergenic.[209]	Rare sensitivity to pumpkin seeds and contact dermatitis reported.[209]
CNS Penetration vs Accumulation	Lipophilic β-carbolines can cross the blood-brain barrier and may accumulate in the central nervous system and liver.[60,66,69,195]	Limited information available; some lipophilic antioxidants may also cross the blood-brain barrier.[191]

cognitive flexibility, as well as changes in BDNF expression, monoamine turnover rates, and oxidative stress markers.[212] Additionally, dual administration may uncover unforeseen neurotoxic effects, tolerance development, or behavioral sensitization-issues that could only be identified through longitudinal preclinical studies.

Dosing Models for Safe Combination

Considering the limited therapeutic window of *P. harmala* and its associated MAO-A inhibition risks,[100] it is crucial to determine safe dosing parameters when used alongside serotonin precursors like tryptophan found in *C. pepo*.

Future research should aim to establish:

- Minimum Effective Doses (MEDs),
- No-Observed-Adverse-Effect Levels (NOAELs),
- Pharmacokinetic interactions involving hepatic enzymes and blood-brain barrier transporters,

Employing a dose-response matrix approach may facilitate the identification of optimal synergistic doses while reducing toxicity risks.

Human Pharmacovigilance

At present, there is no available pharmacovigilance data regarding the clinical use-either combined or separate-of *P. harmala* and *C. pepo* within psychiatric contexts. This absence of data raises concerns for individuals taking SSRIs, SNRIs, or TCAs concurrently.[94]

Ensuring safe practices would necessitate:

- Systematic reporting of adverse events,
- Vigilance against serotonin syndrome and hypertensive crises,
- Establishment of regulatory measures alongside post-marketing monitoring if a formulation becomes available.

Given both plants' traditional uses, unsupervised co-consumption poses a significant risk; thus, public education efforts must be prioritized alongside health policy initiatives.

AI-Guided Synergy Prediction

Artificial Intelligence (AI) and Machine Learning (ML) technologies can serve as effective resources for predicting

interactions among phytochemicals, assessing toxicity levels, and identifying synergistic effects. Recent research has utilized these methods to examine the interactions between *Peganum harmala* and various other plant species, such as Nigella sativa and *Allium nigrum*. This underscores the importance of AI-assisted phytopharmacology in the context of cancer treatment.[213, 214]

Methods such as molecular docking simulations, network pharmacology analysis, and deep learning algorithms focused on synergy prediction can enhance the identification process regarding:

- Common or distinct target binding sites,
- Potential pharmacodynamic antagonisms or synergies,
- CYP450 enzyme interactions or transporter-mediated metabolic pathways.

These advanced modeling approaches minimize dependence on trial-and-error empirical testing while aiding in the strategic design of multi-component herbal therapies.[215]

CONCLUSION

The combination of *Peganum harmala* and *Cucurbita pepo* offers a novel and biologically credible strategy for tackling the complex pathophysiology of neuropsychiatric conditions. By employing complementary mechanisms-such as modulation of monoamines, support for serotonergic synthesis, antioxidant properties, and maintenance of GABAergic balance-this pairing presents a theoretically synergistic effect that may enhance efficacy beyond what either compound could achieve independently. Despite the compelling pharmacodynamic justification, the lack of preclinical synergy studies, toxicological evaluations, and clinical corroboration restricts its current practical application.

In future research, it is vital to implement rigorous experimental frameworks to assess behavioral outcomes, safety limits, and molecular interactions. Given the narrow therapeutic window associated with *P. harmala* and the nutritional safety profile of *C. pepo*, meticulous dose modeling and pharmacovigilance will be essential. Furthermore, utilizing artificial intelligence and systems pharmacology can expedite the discovery of optimal combinations while reducing potential risks.

Until further data becomes available, this combination should be approached as investigational. Nonetheless, it shows considerable promise as a basis for future phytotherapeutic developments aimed at mood disorders and deserves prioritized investigation in the field of translational neuropsychopharmacology.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

MAO-A: Monoamine oxidase A; **BDNF:** Brain-derived neurotrophic factor; **GABA:** Gamma-aminobutyric acid; **ROS:** Reactive oxygen species; **CNS:** Central nervous system; **HPA:** Hypothalamic-pituitary-adrenal; **SSRI:** Selective serotonin reuptake inhibitor; **SNRI:** Serotonin-norepinephrine reuptake inhibitor.

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