

PERSPECTIVE ARTICLE

Exploring *Peganum harmala* as a natural alternative to semaglutide: A novel approach to glucagon-like peptide-1 stimulation and insulin sensitization

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Abstract

Glucagon-like peptide-1 (GLP-1) is a crucial incretin hormone that regulates glucose homeostasis by enhancing insulin secretion, suppressing glucagon release, and delaying gastric emptying. While synthetic GLP-1 receptor agonists such as semaglutide have demonstrated efficacy in managing type 2 diabetes mellitus and obesity, their high cost, limited accessibility, and adverse effects have limited their applicability, necessitating the search for alternative therapeutic strategies. *Peganum harmala* (harmal), a traditional medicinal plant, has gained attention for its bioactive alkaloids, harmine, and harmaline, which have been shown to modulate key molecular pathways involved in GLP-1 secretion and insulin sensitization. These alkaloids enhance Akt phosphorylation (pS473-Akt), facilitating glucose transporter type 4 translocation and glucose uptake, while concurrently activating the nuclear factor erythroid 2-related factor 2 pathway, leading to increased antioxidant defenses and reduced oxidative stress in pancreatic β -cells and enteroendocrine L-cells. Furthermore, *P. harmala* alleviates insulin resistance by suppressing IRS-1 serine phosphorylation (pS307-IRS-1) and improving phosphoinositide 3-kinase/Akt signaling, thereby optimizing insulin receptor sensitivity and metabolic homeostasis. Despite these promising pharmacological properties, the poor solubility and rapid metabolism of harmine and harmaline pose challenges to their clinical application. Nanotechnology-based drug delivery systems, including liposomal encapsulation and polymeric nanoparticles, offer a potential solution to enhance bioavailability, prolong systemic circulation, and enable targeted delivery to GLP-1-secreting cells. This paper delves into the molecular mechanisms by which *P. harmala* stimulates GLP-1 secretion and improves insulin sensitivity, compares its effects with semaglutide, and highlights the potential role of nanotechnology in optimizing its therapeutic applications. By integrating traditional medicine with modern pharmaceutical advancements, *P. harmala* represents a promising, cost-effective, and sustainable approach to metabolic disorder management, warranting further investigation through pre-clinical and clinical studies.

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1. Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by enteroendocrine L-cells in the distal small intestine and colon in response to nutrient ingestion, particularly carbohydrates and lipids. At the molecular level, GLP-1 exerts its effects through the GLP-1 receptor (GLP-1R), a G-protein-coupled receptor widely expressed in pancreatic β -cells, the central nervous system, and peripheral tissues.¹ Upon binding to its receptor, GLP-1 activates the cAMP/protein kinase A (PKA) signaling pathway, leading to enhanced glucose-stimulated insulin secretion, inhibition of glucagon release, and delayed gastric emptying. These actions collectively improve post-prandial glucose homeostasis, making GLP-1 a critical regulator of metabolic processes.²

In addition to its metabolic effects, GLP-1 demonstrates significant neuroprotective properties. Its receptor activation in the brain enhances neuronal survival, reduces oxidative stress, and inhibits neuroinflammatory pathways through modulation of intracellular signaling cascades such as phosphoinositide 3-kinase (PI3K)/Akt and MAPK.³ These properties have positioned GLP-1 analogs as promising therapeutic agents for neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease. Furthermore, GLP-1's ability to suppress appetite and promote weight loss highlights its role in addressing obesity-related metabolic dysfunctions.⁴

Peganum harmala, commonly known as harmal or Syrian rue, has been extensively utilized in traditional medicine across various cultures for its therapeutic properties, particularly in the management of neurological disorders. Historically, harmal has been employed as a remedy for conditions such as epilepsy, anxiety, and insomnia due to its notable psychoactive and neuroprotective effects. The medicinal potential of harmal is attributed to its bioactive alkaloids, primarily harmine, and harmaline, which belong to the β -carboline class of compounds.⁵

Harmine and harmaline exert their effects through multiple molecular mechanisms, including monoamine oxidase inhibition, which elevates neurotransmitter levels such as serotonin, dopamine, and norepinephrine in the central nervous system. This activity underpins harmal's antidepressant and anxiolytic properties. In addition, these alkaloids modulate GABAergic and glutamatergic pathways, contributing to their anticonvulsant effects. Recent studies have also highlighted their neuroprotective potential, which is realized by reducing oxidative stress and inflammation, as well as promoting neuronal regeneration.⁶

This perspective aims to explore the potential relationship between *P. harmala*, a plant with a rich

history in traditional medicine, and the stimulation of GLP-1 secretion. Given the pharmacological significance of GLP-1 as a key regulator of glucose metabolism and its emerging role in metabolic and neurodegenerative disorders, identifying natural agents capable of enhancing GLP-1 secretion has garnered considerable scientific interest. *P. harmala*, known for its bioactive alkaloids, including harmine and harmaline, has demonstrated diverse metabolic and neuroprotective properties that may intersect with GLP-1 pathways. By examining existing evidence, this review seeks to provide a comprehensive overview of the molecular and biological mechanisms through which the herb's influence on GLP-1 secretion. In addition, the implications of this interaction in developing novel therapeutic strategies for diabetes, obesity, and related metabolic dysfunctions are highlighted. This synthesis aims to bridge the gap between traditional medicine and contemporary scientific research, paving the way for future investigations into the therapeutic potential of *P. harmala* in modulating GLP-1 activity.

2. Present evidence on the effects of *P. harmala* on the brain

Recent studies have shed light on the neurotherapeutic potential of *P. harmala*, particularly in enhancing GLP-1 levels in the brain and improving central insulin sensitivity. In a pre-clinical model of AD, *P. harmala* seed extract demonstrated significant efficacy in countering AD-related neurodegeneration, particularly within the hippocampus, a critical region for memory and cognition. The extract increased hippocampal GLP-1 and insulin levels while reducing insulin receptor substrate-1 phosphorylation at serine 307 (pS307-IRS-1), a key marker of insulin resistance. These findings highlight the ability of *P. harmala* to enhance insulin signaling through the activation of Akt phosphorylation at serine 473 (pS473-Akt) and upregulation of glucose transporter type 4 (GLUT4).

In addition to modulating insulin pathways, *P. harmala* reduced the accumulation of pathological markers associated with AD, including beta-amyloid (A β 42), phosphorylated tau, and glycogen synthase kinase-3 β (GSK-3 β). These effects were further augmented by the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) antioxidant pathway, leading to reduced oxidative stress and replenishment of hippocampal glutathione levels. Collectively, these molecular mechanisms underline the dual role of *P. harmala* in mitigating insulin resistance and enhancing GLP-1 signaling, which synergistically improves neuronal glucose uptake and reduces the burden of amyloid pathology in the brain.⁷

Harmine and harmaline, the primary bioactive alkaloids in *P. harmala*, modulate key signaling cascades involved

in neuronal glucose metabolism and insulin sensitivity.^{5,7} Both compounds influence the PI3K/Akt pathway, a critical mediator of cellular survival, growth, and glucose uptake. By enhancing the phosphorylation of Akt at serine 473 (pS473-Akt), harmine and harmaline promote the downstream activation of GLUT4, a transmembrane protein essential for neuronal glucose uptake.⁸

This process begins with the binding of insulin or GLP-1 to their respective receptors, leading to the recruitment and activation of PI3K. PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which acts as a docking site for Akt. Harmine and harmaline potentiate this signaling cascade, ensuring sustained activation of Akt.⁹ The activated Akt phosphorylates downstream targets, including AS160, which facilitates the translocation of GLUT4 vesicles to the neuronal plasma membrane, enhancing glucose uptake into neurons.¹⁰

Harmine and harmaline exert potent antioxidant effects through the activation of the Nrf2 pathway, a master regulator of cellular redox homeostasis.^{5,11} Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is a major contributor to neuronal damage and neurodegeneration.¹² Both harmine and harmaline enhance the nuclear translocation of Nrf2, which is normally sequestered in the cytoplasm by its inhibitor, Kelch-like ECH-associated protein 1 (Keap1).^{5,12}

Upon activation, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to antioxidant response elements in the promoter regions of target genes.¹³ This interaction leads to the upregulation of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase, and catalase. By boosting the production of glutathione and neutralizing ROS, harmine and harmaline reduce oxidative damage to lipids, proteins, and DNA, thereby protecting neurons from oxidative stress-induced apoptosis.^{5,14}

An additional layer of molecular interaction exists between the Akt and Nrf2 pathways, as harmine and harmaline enhance Akt-mediated phosphorylation of GSK-3 β , an inhibitor of Nrf2. This phosphorylation inactivates GSK-3 β , preventing it from targeting Nrf2 for degradation. As a result, harmine and harmaline indirectly amplify Nrf2 activity, creating a synergistic effect that strengthens antioxidant defenses while improving glucose metabolism.^{5,15}

Through the coordinated regulation of the Akt/GLUT4 and Nrf2 pathways, harmine and harmaline exhibit a dual mechanism of action. They not only optimize neuronal glucose uptake and energy utilization but also alleviate

oxidative stress, which is central to the pathophysiology of neurodegenerative diseases. These mechanisms position *P. harmala* as a potential therapeutic agent for disorders characterized by impaired glucose metabolism and elevated oxidative stress, such as AD and other forms of cognitive decline.^{5,7,12,14,15}

3. The systemic importance of GLP-1: Physiological roles and mechanisms

GLP-1 is a multifunctional hormone that plays a central role in maintaining glucose homeostasis and regulating metabolic processes at the systemic level. Synthesized and secreted primarily by enteroendocrine L-cells of the small intestine in response to nutrient ingestion, GLP-1 exerts its effects through the GLP-1R, which is widely expressed in pancreatic islets, the brain, and peripheral tissues.¹⁶

GLP-1 is a critical regulator of blood glucose levels through its glucose-dependent actions on pancreatic β -cells. By binding to GLP-1R, it activates the cAMP/PKA and phospholipase C signaling pathways, leading to enhanced calcium influx and insulin granule exocytosis. This mechanism ensures a precise, nutrient-driven increase in insulin secretion without causing hypoglycemia. Simultaneously, GLP-1 suppresses glucagon secretion from pancreatic α -cells, thereby reducing hepatic gluconeogenesis and further stabilizing blood glucose levels.¹⁷

GLP-1 significantly amplifies the insulinotropic response by increasing the sensitivity of β -cells to glucose. This effect is mediated by upregulating key transcription factors, such as pancreatic and duodenal homeobox 1, which enhances the transcription and translation of insulin.¹⁸

In addition, GLP-1 promotes β -cell proliferation and inhibits apoptosis, contributing to the long-term preservation of pancreatic function, particularly in conditions of metabolic stress such as type 2 diabetes mellitus (T2DM).¹⁹ Beyond its effects on glucose metabolism, GLP-1 plays a pivotal role in the regulation of appetite and body weight. GLP-1R activation in the hypothalamus and brainstem modulates neuronal circuits involved in satiety and hunger. By activating pro-opiomelanocortin neurons and inhibiting neuropeptide Y and agouti-related peptide neurons, GLP-1 reduces food intake and increases feelings of fullness.²⁰ Furthermore, GLP-1 slows gastric emptying through vagal afferent signaling, prolonging the presence of nutrients in the gastrointestinal tract and enhancing satiety signals. These effects collectively contribute to reduced caloric intake and weight loss, making GLP-1 analogs valuable therapeutic agents for obesity and its associated metabolic dysfunctions.²¹

The physiological actions of GLP-1 extend far beyond glucose regulation. Its ability to enhance insulin secretion, suppress glucagon release, and regulate appetite underscores its systemic importance in maintaining energy balance and metabolic health. The therapeutic exploitation of these pathways through GLP-1R agonists (GLP-1RAs) has revolutionized the treatment of T2DM and obesity, while ongoing research continues to uncover its broader roles in cardiovascular and neurological health.²²

4. Present therapeutic applications of GLP-1: Overview and challenges

GLP-1RAs have revolutionized the management of T2DM and obesity, offering significant benefits in glycemic control, weight management, and cardiovascular risk reduction. Agents, such as semaglutide, liraglutide, and dulaglutide mimic the physiological effects of endogenous GLP-1 by enhancing insulin secretion, suppressing glucagon release, and delaying gastric emptying, leading to improved blood glucose levels and weight loss. Semaglutide, in particular, has emerged as a model GLP-1RA due to its long-acting profile and once-weekly administration, which improve therapeutic efficacy and patient compliance.²³ Landmark trials such as SUSTAIN and STEP have demonstrated its efficacy in reducing Hemoglobin A1c, achieving substantial weight loss, and providing cardioprotective benefits by lowering the incidence of major adverse cardiovascular events (MACE) in high-risk populations. Despite these transformative outcomes, the clinical use of GLP-1RAs faces several challenges that hinder their widespread adoption.²⁴

One major challenge is the high cost of GLP-1RAs, attributed to complex manufacturing processes and the substantial investments required for clinical development. This financial barrier disproportionately affects patients in low- and middle-income countries, limiting access to these life-changing therapies. In addition, gastrointestinal side effects, such as nausea, vomiting, and diarrhea, are common, particularly during the early phases of treatment, and may lead to discontinuation for some patients. Rare but severe adverse events, including pancreatitis and gallbladder disease, further necessitate careful patient selection and monitoring. The injectable nature of most GLP-1RAs, such as semaglutide, poses another limitation, as injection-related discomfort or needle phobia can deter treatment adherence. While oral formulations of semaglutide have been developed to address this issue, their slightly reduced bioavailability and efficacy compared to injectable forms present additional clinical considerations.^{25,26}

To address these challenges, ongoing research aims to develop cost-effective manufacturing techniques,

improved formulations to reduce side effects, and innovative delivery systems, such as transdermal patches or advanced oral technologies. Furthermore, the exploration of combination therapies that enhance the efficacy of GLP-1RAs while reducing required doses holds promise for mitigating adverse effects and lowering costs, thereby improving accessibility.

5. Potential development of *P. harmala* extract to stimulate GLP-1 systemically

The therapeutic potential of *P. harmala* in enhancing GLP-1 levels has been primarily explored in the context of brain research, particularly its effects on the hippocampus.⁷ Translating these findings to systemic applications presents a promising avenue for metabolic disease management, such as T2DM and obesity. Studies have demonstrated that the bioactive alkaloids harmine and harmaline in *P. harmala* play pivotal roles in modulating molecular mechanisms critical for GLP-1 stimulation.^{5,7} These mechanisms include the activation of the Akt/GLUT4 pathway, which enhances glucose uptake by promoting Akt phosphorylation at serine 473 and increasing GLUT4 translocation. Furthermore, *P. harmala* significantly reduces oxidative stress by activating Nrf2, a master regulator of antioxidant responses, thereby increasing glutathione levels and reducing lipid peroxidation. This antioxidant effect creates a conducive environment for GLP-1 synthesis and secretion. In addition, *P. harmala* exhibits potent anti-inflammatory effects by mitigating GSK-3 β activity and reducing beta-amyloid accumulation, thereby alleviating neuroinflammation and cellular stress.⁷ These mechanisms, observed in the hippocampus, suggest that harmine and harmaline could similarly stimulate GLP-1 secretion in enteroendocrine L-cells in the gut, the primary site of GLP-1 synthesis. By activating glucose-sensing pathways and protecting L-cells from oxidative and inflammatory stress, *P. harmala* could enhance GLP-1 production and stability systemically. Moreover, the plant's insulin-sensitizing effects, observed in brain studies, could extend to peripheral tissues, improving GLUT4 translocation and reducing insulin resistance.⁷ However, challenges remain in translating these findings into clinical applications, including the need for standardized extracts to ensure consistent alkaloid content, elucidation of gut-specific pathways to confirm their therapeutic potential, and optimization of dosing to balance efficacy and safety given the potential toxicity of *P. harmala* at high doses. With antioxidant, anti-inflammatory, and GLP-1-enhancing properties, *P. harmala* holds significant promise for systemic metabolic regulation and the development of novel therapies targeting GLP-1 pathways.^{5,7,27}

The development of *P. harmala* as an accessible, low-cost natural therapeutic holds significant potential for addressing metabolic disorders by targeting GLP-1 pathways. Unlike synthetic GLP-1RAs such as semaglutide, which are costly and require advanced manufacturing processes, *P. harmala* offers a plant-based alternative with bioactive alkaloids, such as harmine and harmaline that could modulate similar molecular mechanisms. Semaglutide functions by directly mimicking GLP-1, activating its receptor to promote insulin secretion, reduce glucagon release, and delay gastric emptying, thereby improving glycemic control and reducing appetite. However, its systemic distribution requires subcutaneous injection and advanced pharmacokinetic modifications to extend its half-life, increasing production complexity and cost.²⁸

In contrast, *P. harmala* can indirectly enhance GLP-1 levels and activity by targeting upstream pathways. Studies demonstrate that harmine and harmaline stimulate GLP-1 secretion by modulating glucose-sensing mechanisms and reducing oxidative and inflammatory stress in cells. These compounds activate the Akt/GLUT4 pathway, which improves glucose uptake and metabolism, and enhances Nrf2-mediated antioxidant defenses, preserving cellular integrity and functionality. Furthermore, harmine and harmaline mitigate hyperinsulinemia by improving insulin sensitivity, reducing serine phosphorylation of IRS-1, and enhancing downstream signaling pathways.^{7,29} These mechanisms make *P. harmala* a promising natural therapeutic for hyperinsulinemia and GLP-1 stimulation. To enhance the bioavailability and systemic distribution of *P. harmala* alkaloids, nanotechnology offers an innovative solution. Techniques such as encapsulating harmine and harmaline in biodegradable nanoparticles or liposomes could improve their solubility, protect them from enzymatic degradation in the gastrointestinal tract, and allow for controlled release. This approach could enable oral administration with enhanced absorption and targeted delivery to GLP-1-producing L-cells in the gut or pancreatic beta cells, mimicking the localized action of semaglutide.

Moreover, *P. harmala* could be developed as an oral supplement or capsule, with optimized doses of standardized extracts. Pre-clinical studies suggest a dose range of 150 – 200 mg/kg per day for achieving therapeutic effects in metabolic disorders.³⁰ By comparison, semaglutide typically requires weekly doses of 0.5 – 1 mg subcutaneously.³¹ While semaglutide has a longer duration of action due to its synthetic modifications, *P. harmala* could benefit from nanotechnology to achieve sustained release and comparable efficacy with daily oral administration.

The scalability and accessibility of *P. harmala* provide further advantages.

6. Comprehensive evaluation of *P. harmala* in GLP-1 modulation

While the theoretical mechanisms underlying *P. harmala*'s impact on GLP-1 secretion are well-explored, experimental validation remains crucial. Pre-clinical evidence suggests that harmine and harmaline interact with intracellular signaling pathways critical for GLP-1 synthesis and release. In particular, harmine has been shown to promote pancreatic β -cell proliferation by inhibiting dual-specificity tyrosine-regulated kinase 1A, a key regulator of cellular apoptosis.³² Moreover, its influence on incretin-secreting enteroendocrine L-cells remains under investigation, emphasizing the need for targeted *in vivo* studies and controlled clinical trials. Despite promising pre-clinical insights, clinical trials assessing *P. harmala*'s efficacy in metabolic disorders are lacking. Future research must focus on conducting randomized controlled trials to determine its therapeutic potential in managing insulin resistance, obesity, and T2DM. Establishing standardized dosing regimens and long-term safety profiles will be essential for translating these findings into clinical practice.

Harmine and harmaline are believed to modulate GLP-1 secretion through ATP-sensitive K^+ (KATP) channels and calcium-mediated exocytosis.⁷ These alkaloids likely enhance intracellular Ca^{2+} influx through L-type voltage-gated calcium channels, which, in turn, trigger vesicular GLP-1 release.³³ In addition, harmine's interaction with cAMP-response element-binding protein may potentiate *GLP-1* gene expression by upregulating proglucagon transcription, reinforcing its role in incretin hormone synthesis.⁷ High doses of *P. harmala* have been associated with neurotoxic and hepatotoxic effects, largely attributed to excessive β -carboline alkaloid accumulation. *In vivo* toxicity studies reveal that harmine can induce mitochondrial dysfunction through oxidative stress-mediated cytochrome c release, necessitating careful dose optimization. Future studies should aim to delineate the therapeutic window for safe human consumption while implementing nanoparticle-based drug delivery systems to mitigate toxicity risks.³⁴

Nanotechnology holds immense promise in improving the bioavailability of *P. harmala*-derived alkaloids. Liposomal and polymeric nanoparticle formulations can protect harmine and harmaline from enzymatic degradation, ensuring prolonged systemic circulation. Encapsulation techniques utilizing polyethylene glycol (PEG)-modified nanoparticles have demonstrated increased cellular uptake and sustained release, facilitating

targeted GLP-1 stimulation in L-cells and pancreatic β -cells.³⁵ Semaglutide, a synthetic GLP-1RA, directly mimics incretin activity, leading to robust glucose homeostasis regulation. However, its high cost and injectable administration limit widespread accessibility. On the other hand, *P. harmala* offers a plant-based, cost-effective alternative with broader metabolic benefits, including neuroprotection and antioxidative stress reduction. Nevertheless, its lower bioavailability and lack of regulatory approval necessitate further refinement before clinical adoption.

Recent discoveries highlight the interplay between GLP-1 and the gut microbiome, suggesting that modulating microbial composition may enhance endogenous incretin secretion. In addition, novel GLP-1R isoforms with tissue-specific functions are being investigated; presenting opportunities to refine targeted therapies.³⁶ Exploring *P. harmala*'s influence on these pathways could expand its therapeutic scope. The high manufacturing costs of GLP-1RAs pose accessibility challenges, particularly in low-income regions. *P. harmala*'s widespread availability and ease of cultivation position it as a scalable alternative.

Oral semaglutide formulations face significant bioavailability hurdles due to gastrointestinal degradation. Research on absorption enhancers such as sodium N-(8-[2-hydroxybenzoyl]amino) caprylate with the aim to improve uptake efficiency is currently underway.³⁷ Applying similar advancements to oral *P. harmala* formulations may enhance its pharmacokinetic properties, ensuring clinical viability. Beyond metabolic disorders, GLP-1 signaling is implicated in neurodegenerative and cardiovascular conditions.³⁸ Investigating *P. harmala*'s impact on AD, atherosclerosis, and gut-brain axis regulation could unveil novel therapeutic applications.⁷ Furthermore, combinatory approaches involving *P. harmala* and other natural compounds warrant exploration for synergistic metabolic benefits. Notably, *P. harmala* has the potential to revolutionize various treatments by mimicking semaglutide's mechanism of action. This is particularly relevant given the emerging paradigm shift in utilizing semaglutide not only for T2DM but also as a promising therapy for type 1 diabetes, highlighting its broader metabolic and therapeutic implications.³⁹

7. Discussion

The growing body of evidence suggests that *P. harmala*, through its bioactive alkaloids harmine and harmaline, holds significant potential in modulating key molecular pathways associated with glucose homeostasis and insulin sensitivity. Unlike synthetic GLP-1RAs such as semaglutide, which directly activate the GLP-1R, *P. harmala*

appears to exert its effects by stimulating endogenous GLP-1 secretion and enhancing insulin signaling. Harmine and harmaline have been shown to influence GLP-1 synthesis by modulating cellular glucose-sensing mechanisms in enteroendocrine L-cells. Activation of the Akt/GLUT4 pathway plays a pivotal role in this process. By enhancing Akt phosphorylation at serine 473 (pS473-Akt), *P. harmala* facilitates the translocation of GLUT4 to the cell membrane, promoting glucose uptake and increasing intracellular ATP levels. This, in turn, triggers calcium-dependent exocytosis of GLP-1 granules, thereby enhancing the secretion of this incretin hormone. In addition, *P. harmala*'s effects extend beyond direct glucose sensing. The alkaloids modulate oxidative stress and inflammation, two factors that influence GLP-1 secretion. By activating Nrf2, harmine and harmaline upregulate antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, reducing oxidative damage to L-cells and preserving their function. This antioxidant effect contributes to sustained GLP-1 production, making *P. harmala* a promising candidate for enhancing incretin-based therapies. One of the primary mechanisms by which *P. harmala* improves insulin sensitivity is through its interaction with the PI3K/Akt signaling pathway. Insulin resistance, a hallmark of T2DM, is often characterized by impaired Akt activation and GLUT4 translocation. Harmine and harmaline counteract this dysfunction by enhancing PI3K-mediated phosphorylation of Akt, leading to improved downstream insulin signaling, reducing IRS-1 serine phosphorylation (pS307-IRS-1), a key marker of insulin resistance, thereby enhancing insulin receptor sensitivity, and promoting GLUT4 vesicle mobilization, facilitating glucose uptake into peripheral tissues, particularly muscle and adipose cells.⁴⁰ The combined effects of these pathways position *P. harmala* as a potent insulin-sensitizing agent, capable of improving metabolic flexibility and reducing hyperinsulinemia. Beyond its role in insulin signaling, Akt activation indirectly enhances the Nrf2 antioxidant response, creating a synergistic effect that strengthens cellular defense mechanisms. Harmine and harmaline have been shown to inhibit GSK-3 β , an upstream regulator that negatively modulates Nrf2 activity. By inactivating GSK-3 β , *P. harmala* prevents the degradation of Nrf2, thereby amplifying its transcriptional activity and increasing the expression of cytoprotective genes. This interplay between Akt and Nrf2 pathways establishes *P. harmala* as a dual-action therapeutic, simultaneously improving insulin sensitivity and mitigating oxidative stress, both of which are crucial in the pathophysiology of diabetes and neurodegenerative disorders. Despite its promising pharmacological effects, the bioavailability of harmine and harmaline remains a critical challenge.

These alkaloids exhibit poor water solubility and rapid hepatic metabolism, limiting their systemic efficacy. Nanotechnology-based drug delivery systems offer a viable solution by encapsulating harmine and harmaline in liposomes, polymeric nanoparticles, or lipid-based carriers, improving their stability and controlled release, enhancing intestinal permeability, ensuring targeted delivery to enteroendocrine L-cells for GLP-1 stimulation and pancreatic β -cells for insulin secretion, and reducing systemic toxicity, a key consideration given the dose-dependent effects of *P. harmala* alkaloids. By leveraging nanotechnological advancements, the therapeutic potential of *P. harmala* can be optimized, allowing for oral administration with enhanced bioavailability and a more sustained pharmacokinetic profile. While pre-clinical data suggest that *P. harmala* possesses significant metabolic benefits, several challenges must be addressed before its clinical application. One key issue is the standardization of alkaloid content, as variations in harmine and harmaline concentrations across plant extracts necessitate rigorous protocols to ensure consistent therapeutic effects. In addition, long-term safety and toxicity studies are crucial. Despite its historical use in traditional medicine, *P. harmala* exhibits dose-dependent neurotoxic and hepatotoxic risks, requiring comprehensive evaluations. Furthermore, comparative efficacy studies with GLP-1RAs are essential. Direct clinical trials comparing *P. harmala* to semaglutide and other GLP-1 analogs are needed to establish its relative efficacy and pharmacodynamic properties. With ongoing advancements in phytochemical standardization, nanotechnology-based delivery systems, and metabolic disease modeling, *P. harmala* represents a compelling natural candidate for the future of incretin-based and insulin-sensitizing therapies⁴¹

8. Conclusion

P. harmala presents a compelling natural alternative for enhancing GLP-1 secretion, improving insulin sensitivity, and mitigating oxidative stress, offering a novel therapeutic avenue for metabolic disorders. Across its bioactive alkaloids, particularly harmine and harmaline, *P. harmala* exerts multifaceted pharmacological effects, modulating key molecular pathways involved in glucose metabolism, pancreatic β -cell protection, and systemic insulin regulation. Furthermore, advancements in nanotechnology provide a promising strategy to overcome bioavailability limitations, ensuring its therapeutic efficacy. While the potential of *P. harmala* as a metabolic therapeutic is evident, further research is required to bridge the gap between pre-clinical findings and clinical application. Rigorous investigations, including randomized controlled trials, standardized dosing studies, and long-term safety assessments, are imperative to

establish its clinical viability. Moreover, exploring its synergy with existing GLP-1RAs and its broader implications in neurodegenerative and cardiovascular diseases could unlock additional therapeutic opportunities.

By integrating traditional medicine with modern biomedical innovations, *P. harmala* holds the promise of transforming metabolic disorder management. Its affordability, accessibility, and natural origin make it a valuable candidate for global healthcare strategies, particularly in regions where conventional GLP-1RAs remain financially and logistically restrictive. Moving forward, interdisciplinary collaborations between pharmacologists, endocrinologists, and nanotechnology experts will be crucial in realizing the full therapeutic potential of *P. harmala*, paving the way for its integration into evidence-based clinical practice.

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Author contributions

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