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Pharmacological and therapeutic properties of *Peganum harmala* L. (Syrian rue)

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***Peganum harmala*, commonly known as Syrian rue, African rue, wild rue, harmel, or esfand, is a medicinal plant highly valued for its rich composition of bioactive phyto-constituents. It is particularly abundant in naturally occurring alkaloids such as β-carboline, harmalol, harmaline, and harmine, with harmine being the most extensively studied. This plant exhibits a wide spectrum of biological activities, including antifungal, antimicrobial, antibacterial, antidiabetic, anti-inflammatory, anticancer, hypothermic, analgesic, abortifacient, anthelmintic, cytotoxic, and hallucinogenic effects. Such diverse pharmacological properties make *P. harmala* a significant plant of interest for therapeutic applications and further drug discovery.**

Key words: *Peganum harmala*; alkaloids, pharmacological properties; medicinal and traditional uses.

INTRODUCTION

Medicinal plants have intrigued humans since ancient times, with nearly every civilization maintaining a long history of their use in healthcare. They have historically played a vital role in primary healthcare systems and have significantly contributed to the discovery and development of modern medicines (Shabana et al., 2023). Globally, it is estimated that around 80% of the population relies on traditional medicine, of which nearly 85% of treatments involve plant-derived extracts (Bapat et al., 2008). *Peganum harmala* L., commonly known as Syrian rue, is a perennial medicinal herb belonging to the family Nitrariaceae. It is native to Central Asia and is widely distributed across semi-arid regions of North-West India, Central Asia, and North Africa (Sharifi-Rad et al., 2021; Vahabzadeh et al., 2019). The plant is particularly rich in active constituents, primarily concentrated in its fruits and seeds, which are known for their diuretic, hallucinogenic, digestive, hypnotic, antispasmodic, antipyretic, emetic, narcotic, and uterine stimulant properties. The leaves of *P. harmala* are traditionally used to treat ailments such as colic, hiccups, dysmenorrhea, hysteria, neuralgia, asthma, and rheumatism. Furthermore, seeds of the plant yield a red dye that has been widely used in Iran and Turkey for coloring carpets and textiles (Sharifi et al., 2021).

METHODOLOGY

This comprehensive review aims to bridge the gap between traditional uses and modern therapeutic properties of *P. harmala*. It highlights the botanical description and health-promoting effects

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of this plant. The compilation is done after profound literature search by using the multiple databases, such as PubMed, Scopus, Web of Science, and Google Scholar.

RESULTS AND DISCUSSION

P. harmala is a perennial ,ranging from 30 to 70 cm in height. It is erect to spreading and heavily branched from the base, with a glabrous (smooth and hairless). The roots can be up to 2 cm in diameter. leaves are alternate, with ovate blades divided in 3 to 5 linear to lanceolate-linear lobes measure 1 to 3.5 × 1.5 to 3 mm. Flowers are opposite leaves on apical parts of the branches. The plant has five sepals, divided into linear lobes, 1.5 to 2 cm long, sometimes only divided at the apex. There are five petals, yellow to white, obovat to oblong, measuring 15 to 20 × 6 to 9 mm. There are 15 stamens with enlarged filament bases. The ovary is three-locular, and the capsule is globular. The seeds are dark brown, slightly curved, three-angled, and have a muriculate (warty). Flowering occurs from May to June, and fruiting from July to November. (Source: efloras.org)

Active constituents

This plant contains numerous pharmacologically significant active compounds. Notably, it harbors several alkaloids, including β-carbolines (harmaline,harmine, also known as harmidine) and derivatives of quinazoline (vasicine and vasicinone). Ripe seeds exhibit a markedly higher alkaloid concentration compared to unripe ones.

Harmaline

Harmaline, a major alkaloid derived from *P. harmala*, exhibits strong biological activity. It is known to produce symptoms such as tremors and colonic convulsions, notably without enhancing spinal reflex excitability—implying a targeted effect on the central nervous system. At toxic doses, harmaline can cause severe convulsions followed by motor paralysis, reflecting its profound depressant impact on neural function. Additionally, it has been shown to lower blood pressure over a broad dosage range, primarily due to its marked weakening effect on cardiac muscle.

Harmine

Harmine, also known as Banisterine, is a significant alkaloid found in *P. harmala* as well as in several other plant species, including *Banisteria caapi*, *Diplopterys lutea*, and *Banisteriopsis muricata*. Although pharmacologically similar to harmaline, harmine is generally considered less toxic, making it a safer for therapeutic use. Notably, the hydrochloride salt of harmine has demonstrated potent antibacterial activity against *Mycobacterium tuberculosis*, underscoring its potential as a medicinal agent in the treatment of tuberculosis (Mahmoudian et al., 2002).

Harmalol

Harmalol is a naturally occurring β-carboline alkaloid, primarily found in the seeds of the *P. harmala* it belongs to a group of compounds known for their psychoactive, antioxidant, and potential therapeutic properties (El Gendy et al., 2012; Moloudizargari et al., 2013)

Vasicine

Vasicine, also known by the name peganine, is a quinazoline alkaloid primarily extracted from the leaves of *Justicia adhatoda* (Acanthaceae), commonly known as "vasaka." It is also found in *P. harmala* has been studied for its bronchodilatory and uterotonic properties. Traditionally, it has been used in the management of respiratory ailments such as asthma and bronchitis. Vasicine exhibits strong expectorant and antitussive activity, which justifies its traditional use in treating pulmonary disorders. However, its uterotonic effects also warrant caution, particularly in pregnancy, due to the risk of stimulating uterine contractions (Moloudizargari et al., 2013; Iranshahy et al., 2019).

Vasicinone

Vasicinone, a derivative of vasicine, demonstrates similar pharmacological activities but with comparatively milder effects. It exhibits bronchodilatory, anti-inflammatory, and antispasmodic properties, contributing to its therapeutic potential in respiratory conditions. Interestingly, when combined with vasicine, vasicinone shows synergistic bronchodilatory activity, which has been explored in the development of herbal formulations for asthma and related disorders (Basu et al., 2011).

Traditional and historical uses of *P. harmala*

In ancient Greece, powdered seeds were employed to treat tapeworm infections and recurring fevers, which were most likely associated with malaria. emonstrates deep historical/ethnobotanical use of *P. harmala* as a psychoactive/medicinal fumigant useful for lecture material on ethnobotany, archaeochemistry, and cultural uses of medicinal plants (Table 1) (Huber et al., 2025).

Pain relief and anti-inflammatory action

Traditionally, *P. harmala* has been employed as a natural remedy for pain management and inflammation, making it

Table 1. Traditional ethanomedicinal, and cultural uses of *P. haramala* across different regions of the world.

Plant part used	Traditional use	Region/Culture
Seeds	Burned as incense to ward off the “evil eye” and for spiritual/ritual ceremonies	Middle East, Central Asia, North Africa
Seeds (powder/extract)	Analgesic, anti-inflammatory; treatment of rheumatism and joint pain	Central Asia, India
Seeds (smoke/decoction)	Relief of asthma, cough, and bronchitis	Iran, Afghanistan, North-West India
Seeds (ingested)	Anthelmintic (expulsion of intestinal parasites) and digestive aid for colic and indigestion	Traditional Persian and Ayurvedic medicine
Leaves	Treatment of colic, hiccups, dysmenorrhea, hysteria, neuralgia, and asthma	Folk medicine across Central Asia and India
Fruit/Seeds	Used as a hallucinogen and antidepressant; management of insomnia and hysteria	Middle East, Mediterranean regions
Seed paste/extract	Applied topically for skin infections, wounds, psoriasis, and inflammation	North Africa, India
Seeds (ripe)	Source of a red dye for coloring carpets and textiles	Iran, Turkey

useful in alleviating aches, swelling, and related conditions (Splettstoesser et al., 2005; Rezaei et al., 2016).

Neurological applications

The plant has a long history of use in treating neurological disorders, particularly Parkinson’s disease**.** Its alkaloids possess neuroprotective properties**,** helping protect nerve cells from damage caused by excessive dopamine and glutamate (Splettstoesser et al., 2005).

Gastrointestinal and cardiovascular health

In folk medicine, *P. harmala* has been used to address digestive disturbances and cardiovascular problems, reflecting its importance in supporting internal health (Splettstoesser et al., 2005; Rezaei et al., 2016).

Cancer and tumor treatment

Ethnomedicinal records show its application in managing certain forms of cancer**.** For example, in Morocco, ground seeds have been traditionally used in the treatment of skin and subcutaneous tumors (Moura et al., 2007; Tahraoui et al., 2007).

Mental health and antimicrobial potential

In Yemen, the seeds have been traditionally prescribed for depression**.** The active alkaloid harmaline functions as a central nervous system stimulant and a reversible inhibitor of monoamine oxidase-A (RIMA**)**, giving it antidepressant properties (Pathan et al., 2012). Moreover, *P. harmala* extracts exhibit activity against antibiotic-resistant bacteria**,** highlighting its potential in addressing modern health challenges.

Pharmacological activities of *P. harmala*

Anticancer activity

The β-carboline alkaloids present in *P. harmala* (such as harmine and harmaline) have shown strong anticancer potential. They inhibit (DNA) topoisomerases**,** disrupt DNA synthesis, and possess antioxidant and antimutagenic properties, making them valuable in cancer research (Table 2) (Lamchouri, 2014; Sharma et al., 2016; Muddather et al., 2025).

Anthelmintic and antimicrobial properties

The seed smoke of *P. harmala* has been used traditionally to kill algae, bacteria, molds, and intestinal parasites. This antimicrobial action is especially effective against drug-resistant strains. It also acts as an anthelmintic, helping to expel parasitic worms (Niroumand et al., 2015).

Effects on reproductive health

It has abortifacient activity and can negatively affect male

Table 2. Therapeutic properties of *P. harmala* bioactive compounds and their pharamacological effects

Activity	Active compounds/Extracts	Effects/Mechanism	References
Anticancer	β-carboline alkaloids (harmine, harmaline)	Inhibit DNA topoisomerases, interfere with DNA synthesis, antioxidant and antimutagenic	Lamchouri (2014)
Anthelmintic and antimicrobial	Seed smoke, alkaloids	Kills algae, bacteria, molds, intestinal parasites; expels worms; effective vs. drug-resistant bacteria	Niroumand et al. (2015)
Historical use	Powdered seeds	Used in ancient Greece against tapeworms and fevers (likely malaria-related)	–
Reproductive effects	Harmine, harmaline, others	Abortifacient; high doses reduce spermatogenesis and fertility in rats	Khan et al. (2017)
Cardiovascular	Harmine, harmaline, harman, harmalol	Bradycardia, ↓ blood pressure, ↓ vascular resistance, ↑ cardiac contractility, vasorelaxant, angiogenesis inhibition	Hamsa and Kuttan (2010) and Moloudizargari et al. (2013)
Vasorelaxant/ Antihypertensive	Harmine > Harmaline > Harmalol	α1-adrenergic interaction; ↑ nitric oxide release; ↓ arterial pressure and resistance	Shi et al. (2000), Berrougui et al. (2006) and Khaliq et al. (2009)
Angiogenesis inhibition	Harmine	Inhibits endothelial proliferation, VEGF, NO, cytokines; blocks NF-κB, CREB, ATF-2; ↓ COX-2, iNOS, MMPs	Hamsa and Kuttan (2010)
Antiprotozoal	Harmine, Harmaline, Peganine	Weak activity (harmine, harmaline); harmaline toxic to amastigotes; Peganine effective vs. *Leishmania donovani* (100 mg/kg in hamsters)	Di Giorgio et al. (2004), Mirzaie et al. (2007), Khaliq et al. (2009) and Yonezawa et al. (2011)
Antibacterial	Harmine; Methanolic extracts	Strong activity vs. *Proteus vulgaris, Bacillus subtilis, S. aureus, P. aeruginosa, E. coli, K. pneumoniae*; potential vs. antibiotic-resistant strains	Nafisi (2011), Rharrabe et al. (2007) and Moloudizargari et al. (2013)
Antifungal	Crude alkaloids	Effective vs. *Aspergillus niger, Candida albicans*; MIC = 0.333 ± 0.007 mg/ml	Nenaah et al. (2010)
Insecticidal	Harmaline; Methanolic extracts	Harmaline blocks larval development of *Plodia interpunctella*; methanolic extract toxic to *Tribolium castaneum* larvae	Jbilou et al. (2008)
Osteogenic	Harmine	Inhibits osteoclasts (↓ c-Fos, NFATc1); promotes osteoblast differentiation (↑ BMP, Runx2 pathway); structure-activity role of C3–C4 double bond and 7-methoxy group	Waki et al. (2007), Yonezawa et al. (2011), Moloudizargari et al. (2013) and Vahabzadeh et al. (2019)
Antidiabetic	Harmine	Hypoglycemic effect; regulates PPARγ (key target in adipogenesis and diabetes drugs); effect lost at high doses	Fortunato et al. (2009), Pathan et al. (2012), Niroumand et al. (2015) and Sharifi-Rad et al. (2021)

fertility. In experimental studies on rats, high doses reduced spermatogenesis and overall reproductive potential (Khan et al., 2017). This highlights the importance of careful use.

1) Cardiovascular effects: Traditionally, *P. harmala* has been used to manage hypertension and heart-related conditions. Its alkaloids (harmine, harmaline, harman, harmalol**)** show lowering of

blood pressure; bradycardia (slowed heart rate); reduced vascular resistance, improved cardiac contractility and pulse pressure (Hamsa and Kuttan, 2010; Moloudizargari et al., 2013).
2) Vasorelaxant and antihypertensive action: The seed extract reported to show *antispasmodic,* anticholinergic, antihistaminic, and antiadrenergic activities (Shi et al., 2000). Among its alkaloids, harmine is the most potent vasodilator, followed by harmaline and harmalol**.** These compounds act mainly by interacting with α1-adrenergic receptors in vascular smooth muscles and by stimulating nitric oxide (NO) release, which lowers blood pressure (Berrougui et al., 2006; Khaliq et al., 2009).
3) Angiogenesis inhibition: Harmine strongly suppresses new blood vessel formation**,** which is important in both cancer progression and cardiovascular diseases. It achieves this by: Inhibiting endothelial cell proliferation; Reducing pro-angiogenic factors (VEGF, NO, cytokines) Blocking transcription factors like NF-κB, CREB, ATF-2**,** Lowering tumor production of COX-2, iNOS, and matrix metallo-proteases (Hamsa and Kuttan, 2010).

Antiprotozoal activity

It *s*hows promising results against *Leishmania* parasites: Harmine and harmaline: weak activity against promastigotes and amastigotes; Harmaline- strong toxicity against amastigotes inside macrophages; Peganine-highly effective in treating visceral leishmaniasis; a dose of 100 mg/kg cured *Leishmania donovani* infections in hamsters (Di Giorgio et al., 2004; Mirzaie et al., 2007; Khaliq et al., 2009; Yonezawa et al., 2011).

Additional pharmacological activities of *P. harmala*

Antibacterial activity

Alkaloids of *P. harmala* demonstrate strong antibacterial effects, often comparable to common antibiotics but with fewer side effects. Sensitive organisms: *Proteus vulgaris* and *Bacillus subtilis* show high sensitivity to harmine (Nafisi, 2011); Extract comparison: Methanolic extracts exhibit greater antibacterial potency than chloroform and petroleum extracts, particularly against *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae,* and *P. vulgaris*. *P. harmala* alkaloids may help in controlling antibiotic-resistant bacterial strains (Rharrabe et al., 2007; Arshad et al., 2008; Moloudizargari et al., 2013).

Insecticidal and antifungal activities

P. harmala extracts and alkaloids display broad antifungal and insecticidal properties: Antifungal: Effective against *Aspergillus niger* and *Candida albicans* with a minimal inhibitory concentration (MIC) of 0.333 ± 0.007 mg/ml (Nenaah, 2010). Insecticidal: Harmaline inhibits the development of *Plodia interpunctella* (stored food pest) by destroying midgut epithelial cells. Methanolic extracts exhibit significant toxicity to *Tribolium castaneum* (stored grain pest) when added to the diet (Jbilou et al., 2008). Thus, *P. harmala* could serve as a valuable eco-friendly pest control agent.

Osteogenic activity

Harmine, a key alkaloid of *P. harmala*, has been shown to possess bone anabolic properties; Inhibition of bone resorption: Harmine suppresses osteoclast formation by down-regulating c-Fos and NFATc1, thereby preventing osteoclast-mediated bone loss (Yonezawa et al., 2011) Promotion of bone formation**:** It enhances osteoblast differentiation by inducing bone morphogenetic protein (BMP) expression and activating the Runx2 pathway; Structure-activity relationship: The C3 to 4 double bond and 7-methoxy group of harmine are crucial for its osteogenic effects (Waki et al., 2007; Moloudizargari et al., 2013; Vahabzadeh et al., 2019).

Antidiabetic effect

Traditionally, *P. harmala* has been used for diabetes management in various cultures. Modern studies confirm its hypoglycemic activity: Efficacy: Harmine is the main alkaloid responsible for lowering blood glucose levels. However, very high doses may reduce effectiveness (Pathan et al., 2012; Moloudizargari et al., 2013) Mechanism**:** Harmine regulates peroxisome proliferator-activated receptor gamma (PPARγ)**,** a major regulator of adipogenesis and a target of thiazolidinedione antidiabetic drugs (Waki et al., 2007; Sharifi-Rad et al., 2021) Significance- This suggests *P. harmala* could serve as a natural antidiabetic agent**,** though dose standardization is crucial.

Conclusion

P. harmala (Syrian rue) is a highly versatile medicinal plant with a broad spectrum of pharmacological activities. This plant continues to play an essential role in healthcare systems worldwide, supporting both disease treatment and health maintenance. Its bioactive compounds**,** particularly the β-carboline alkaloids (harmine, harmaline, harmalol), exhibit a wide range of therapeutic effects including anticancer, cardiovascular, antiprotozoal, antibacterial, insecticidal, antifungal, osteogenic, and antidiabetic properties (Table 2). These activities underscore its potential in addressing diverse health conditions, from infectious diseases to chronic disorders such as cancer and diabetes. The long history and rich pharmacological profile of *P. harmala* highlight the enduring relevance of traditional medicine and offer valuable leads for natural product-based drug development. By bridging traditional knowledge with

modern scientific approaches, this plant holds promise as a source of novel therapeutic agents to tackle both present and emerging health challenges.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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