Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids

Milad Moloudizargari, Peyman Mikaili[1], Shahin Aghajanshakeri, Mohammad Hossein Asghari, Jalal Shayegh[2]

Student of Veterinary Medicine, Faculty of Veterinary Medicine, Urmia University, [1]Department of Pharmacology, Faculty of Pharmacy, Urmia University of Medical Sciences, Urmia, [2]Veterinary Medicine, Faculty of Agriculture and Veterinary, Shabestar Branch, Islamic Azad University, Shabestar, Iran

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ABSTRACT

Wild Syrian rue (*Peganum harmala* L. family Zygophyllaceae) is well-known in Iran and various parts of this plant including, its seeds, bark, and root have been used as folk medicine. Recent years of research has demonstrated different pharmacological and therapeutic effects of *P. harmala* and its active alkaloids, especially harmine and harmaline. Analytical studies on the chemical composition of the plant show that the most important constituents of this plant are beta-carboline alkaloids such as harmalol, harmaline, and harmine. Harmine is the most studied among these naturally occurring alkaloids. In addition to *P. harmala* (Syrian rue), these beta-carbolines are present in many other plants such as *Banisteria caapi* and are used for the treatment of different diseases. This article reviews the traditional uses and pharmacological effects of total extract and individual active alkaloids of *P. harmala* (Syrian rue).

Key words: Harmine, harmaline, *peganum harmala*, pharmacological effects, wild syrian rue

INTRODUCTION

Harmal[1] (*Peganum harmala* L. family *Zygophyllaceae*) is a perennial, glabrous plant which grows spontaneously in semi-arid conditions, steppe areas and sandy soils, native to eastern Mediterranean region. It is a shrub, 0.3-0.8 m tall with short creeping roots, white flowers and round seed capsules carrying more than 50 seeds. The plant is well-known in Iran and is widely distributed and used as a medicinal plant in Central Asia, North Africa and Middle East.[2-5] It has also been introduced in America and Australia. Dried capsules – mixed with other ingredients – are burnt as a charm against "the evil eye" among Iranians.[2] This plant is known as "Espand" in Iran, "Harmel" in North Africa and "African rue," "Mexican rue" or "Turkish rue" in the United States.[6] Various parts of *P. harmala* including its seeds, fruits, root, and bark, have been used as folk medicine for a long time in Iran and other countries [Table 1]. Many pharmacological surveys have shown different effects of *P. harmala* [Table 4] and/or its active alkaloids (particularly harmaline) [Table 5].

Studies carried out on the chemical composition of the extracts show that beta-carboline and quinazoline alkaloids are important compounds of this plant [Figure 1]. In one study, the concentration of harmaline in different parts of the plant including seeds, fruits, and capsule walls was determined by Reverse phase high-performance liquid chromatography (RP-HPLC) as 56.0 mg/g, 4.55 mg/g and 0.54 mg/g, respectively.[7] Although, harmaline and harmine are the most important alkaloids that are generally responsible for their beneficial effects, numerous studies show that other alkaloids present in *P. harmala* also have some roles in the pharmacological effects of the plant.[8] Harmaline ($C_{13}H_{15}ON_2$) was first isolated by Göbel from the seeds and roots of *P. harmala* and is the major alkaloid of this plant.[6] In addition to *P. harmala* (Harmal), beta-carboline alkaloids are present in many other plants such as *Banisteriopsis caapi* (*Malpighiaceae*). They are also constituents of Ayahuasca, a hallucinogenic beverage ingested in rituals by the Amazonian tribes.[7] This article completely reviews the pharmacological effects of *P. harmala* [Table 2] and its active ingredients [Table 3].[6,7]

Address for correspondence:
Mr. Milad Moloudizargari, Veterinary School, Urmia University, Urmia, Iran.
E-mail: miladmoludi@gmail.com

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Table 1: Traditional uses of *Peganum harmala*

System	Effects	Part of plant	Preparation	Country	References
Cardiovascular	Antihypertensive in cardiac diseases	Seeds	Not determined	Morroco	[87]
	Antihypertensive	Seeds	Infusion/powder	Morroco	[9]
	Hypotensive	Seeds	Powder/infusion	Morroco	[70]
	Hypotensive			Italy/Tunisia	[19]
	Antihypertensive	Seeds		Morroco	[88]
	Hypotensive, blood purifier	Seeds		Jordan	[20]
Gasterointestinal	To treat diarrhea and intestinal pain	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	Antispasmodic in colic	Seeds	Powdered/various extracts		[40]
	Antidiarrheal, bowels diseases, antispasmodic	Seeds	Powder/infusion	Morroco	[70]
	Astringent		Internal use	Jordan	[89]
	To treat intestinal pain	Seeds	Eaten	Turkey	[29]
	Antispasmodic, emetic		Extracts		[43]
Nervous	Antiparkinson				[19]
	Against nervosity	Seeds		Jordan	[20]
	In psychiatric conditions				[7]
	Narcotic, analgesic	Seeds	Powdered/various extracts		[40]
	Against depression			Yemen	[90]
	Hallucinogenic, nervous diseases	Seeds	Powder/infusion	Morroco	[70]
	Sciatica	Seeds	Seeds ground with ginger, honey and some water for external massage		[46]
	Antiparkinson			Italy and Tunisia	[19]
	Nervisity	Seeds		Jordan	[20]
	Syrian rue seeds have been used for centuries as psychoactive drugs, having represented the “haoma” of the old Persian Zoroastrian ceremonies	Seeds		Iran	[29]
	The plant has also been considered as a possible (although doubtful) candidate for the mysterious Soma described in the Rig-Veda or the haoma of the old Persian Zoroastrian ceremonies			Central America, Central Asia and Syria	[2]
	Psychological effects				[6]
Endocrine	Abortion	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	Emmenagogue	Seeds	Poeder/infusion	Morroco	[70]
	Emmenagogue and an abortifacient agent			Middle East and North Africa	[2,6]
	Emmenagogue and an abortifacient agent		Extracts		[43]
Neoplasm and tumors	Subcutaneous tumors	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	For treatment of neoplasms	Seeds		Iran	[66]
Pain relieving	As a remedy of dolorous events (rheumatic pain, painful joint and intestinal pain)+lumbago	Seeds	Powder, decoction, maceration or infusion		[21]
	Anagesic	Seeds	Powdered seeds and various extracts		[40]
	Back pain	Seeds		Jordan	[20]
	To treat intestinal pain	Seeds	Eaten	Turkey	[29]
	Antalgic	Seeds	Powdered/infu sion	Morroco	[70]

Contd...

Table 1: Contd...

System	Effects	Part of plant	Preparation	Country	References
	Articulation pain	Seeds	Ground with ginger, honey and some water for external massage		[46]
Organisms	Against tape-worm infection in man and animals	Seeds	Powdered seeds and various extracts		[40]
	Anthelmintic/Antimicrobial	Seeds	Powdered/infusion	Morroco	[70]
	Antibacterial			Turkey	[35]
	Leishmaniasis	Full plant	External use only	Spain	[48]
	Leishmaniasis	Seeds	Ground with ginger, honey and some water for external massage		[48]
	Anti-fungal				[42]
	Antiparasidal				[46]
	Anthelmintic		Extracts		[43]
	To get rid of tape-worms	Seeds	Powdered	Greece	[90]
Diabetes	Antidiabetic (mellitus)	Seeds	Not determined	Morroco	[87]
	Antidiabetic/hypoglyce mic	Seeds	Infusion/powd ered	Morroco	[9]
	To treat diabetes	Seeds		Morroco	[88]
Respiratory	Asthma	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	In bronchitis/expectorant/ asthma	Seeds/A P	Ethanol extract of	India	[35]
Disinfectant	Air purifier	Fruit	SI/ES?	Iran/Uzbekis tan	[91]
	Antiseptic/disinfectant		Smoke		[86]
	Air purifier	Dried capsules (known as espænd or esfændd a neh) – mixed with other ingredie nts	Are burnt so as to produce a scented smoke that is used as an air purifier	Iran	[2]
Anti-pyretic	In fever	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	As febrifuge		Internal use	Jordan	[89]
	Antipyretic		Extracts		[43]
	To treat recurring fevers (specially malaria)	Seeds	Powdered	Greece	[90]
Skin and hair	Dermatologic	Full plant	External use only	Spain	[48]
	Dermatologic	Seeds	Ground with ginger, honey and some water for external massage		[48]
	For treatment of skin disease				[86]
	Hair care	Seeds	Powder/infusion	Morroco	[70]
Rheumatism, arthritis and inflammation	Rheumatic pain, painful joint	Seeds	Powder, decoction, maceration or infusion	Morroco	[21]
	Antirheumatic	Seeds	Powder/infusion	Morroco	[70]
	To treat Inflammation	Full plant	External use only	Spain	[48]
	Articulation pain, rheumatism and sciatica	Seeds	Ground with ginger, honey and some water for external massage		[48]
	Arthritis	Seeds		Jordan	[20]
Ulcers	Cicatrizing	Seeds	Powder/infusion	Morroco	[70]
	Vulnerary	Full plant	External use only	Spain	[48]
	Healing ulcers	Seeds		Jordan	[20]
Other	Asthenia	Seeds	Powder/infusion	Morroco	[70]
	Relief cold	Fruit	SI/ES	Iran/Uzbekis tan	[91]
	common cold/impotence	Seeds		Jordan	[20]
	Lactagogue		Extracts		[43]
	As a dye			Central Asia, Syria	[92]

Contd...

Table 1: Contd...

System	Effects	Part of plant	Preparation	Country	References
	Jaundice	Seeds	Powder, decoction, maceration or infusion		[21]
Believes	As a magic	Seeds	Powder/infusion	Morroco	[70]
	Amulet against evil-eye	Fruits	Dried, in necklaces (sometimes also a bench of the plant is hung in the house)	Turkey	[29]
	As a charm against ''the evil eye''		Dried capsules (known as espænd or esfændda-neh)-mixed with other ingredients-are burnt so as to produce a scented smoke	Iran	[2]

ES=Erowid syrian rue, SI=Smoke inhalation, AP=Aerial parts

Table 2: Pharmacological effects of *Peganum harmala*

System	Effects	Part of plant	Preparation	References
Cardiovascular	Antispasmodic, anticholinergic, antihistaminic and antiadrenergic	Seeds	Aqueous extract	[14]
Nervous system	Inhibition of MAO-A	Seeds and root	Extract	[7]
	Inhibition of COMT		Extract	[34]
	Analgesic		Ethyl acetate, butanolic and aqueous extracts	[21,23,35]
Antimicrobial	Antifungal: *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger and Candida albicans*		Methanolic, aqueous and chloroform extract	[42]
	Antileishmanial activity (against L. major) (the same potency as antimonyl tartrate)		Extract	[48]
	Decreases the lesion size and number of the parasites in cutaneous leishmaniasis		Extract	[49]
Antimicrobial	Antitheileriosis		Extract	[51],[52]
	Antibacterial: *S. aureus, P. aeruginosa, E. coli, K. pneumoniae, and P. vulgaris*		Methanolic extract	[43]
	Aspergillus niger and Candida albicans		Crude extract	[41]
	Against *Tribolium castaneum*, the stored grain pest (larvae and adult)		Extract	[45]
	Against: Algae, intestinal parasites, molds, bacteria, insects, lice	Seeds	Smoke	[90]
	Antibacterial: *Streptococcus pyogenus*	Leaves	Methanolic extract	[90]
Antineoplasm	Antibacterial: *S. aureus, P. aeruginosa , E. coli, K. pneumoniae, P. vulgaris*	Seeds	Extracts: Petroleum ether fraction, chloroform fraction, methanolic fraction	[43]
	Antitumor (cell lines: UCP-Med, Med-mek carcinoma, and UCP-Med sarcoma)		Methanolic extract and total extract	[93]
	Inhibits human DNA Topoisomerase I		Extract	[61]
	Antioxidant and free radical scavenging effect (via increasing the level of 17β-estradiol)		Extract	[62,63,64]
	NSE and TG levels in animal models (anticarcinogenecity effect)		Ethanol and chloroform extracts	[65]
	Anti-proliferative effect on Leukemic cell lines		Extract	[66]
	Inhibitory action on the metastasis of melanoma cells, inducing apoptosis in melanoma cells		Extracts	[67]
Antineoplasm	Angiogenesis inhibition		Extract	[13]
	Binding to RNA		Extract	[59]
	Anti-inflammatory (via the inhibition of some inflammatory mediators)		Extract	[48]
	Inducing abdominal writhing, body tremors and slight decrease in locomotor activity		Extracts	[21]

MAO-A=Mostly harmine and harmaline, COMT=Catechol-O-methyltransferase, S. aureus=*Staphylococcus aureus*, *P. aeruginosa=Pseudomonas aeruginosa, E. coli=Escherichia coli, K. pneumonia=Klebsiella pneumonia, P. vulgaris=Proteus vulgaris*, UCP-Med=UCP-Med carcinoma (a tumor cell line), DNA=Deoxyribonucleic acid, RNA=Ribonucleic acid, NSE=Normalize neuron-specific enolase, TG=Thyroglobulin

Table 3: Pharmacological effects of alkaloids of *Peganum harmala*

System	Effect	Reference
Cardiovascular and blood	Bradycardia	[10]
	Decreasing systemic arterial blood pressure	
	Decreasing total peripheral vascular resistance	
	Increasing pulse pressure	
	Increasing peak aortic flow	
	Increasing cardiac contractile force (harmine, harmaline, harmalol)	
	Vasorelaxant (harmine, harmaline, harmalol, harman)	[11,12,15]
	Angiogenic inhibitory effect	[13]
	Increasing effect on NO release from the vascular endothelial cells (harmine, harmaline, harman)	[11,15]
	Hypotensive (harman, harmaline, etc.)	
	Activation of prostacyclin pathway (harmaline)	[12]
	Vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta (vasicinone)	[16]
	Inducing transient hypotension and long-lasting bradycardia (harman)	[11]
	Inhibition of both $45Ca^{2+}$uptake and efflux in cardiac sarcolemal vesicles (dose-dependent) (harmaline)	[17]
	Reduces expression of pro-angiogenic factors (VEGF-NO) and pro-inflammatory cytokines and (harmine)	[13]
	Inhibition of angiogenesis (harmine)	
Nervous system	Analgesic (all alkaloids)	[21]
	Hallucinergic	[24]
	Excitatory	
	Anti-depressiv	[25]
	Interaction with receptors	[21,24,31,32]
	Opioid	
	Dopamine	
	GABA	
	5-hydroxytryptamine	
	Benzodiazepine	
	Imidazoline	
	Inhibition of monoamine oxidase (MAO-A) (mostly harmine and harmaline)	[25]
	Increasing BDNF protein levels (harmine)	
	Inhibition of MAO-B and anti-Parkinsonism (norharman and 9methylnorharman, harmine and harmaline)	[33,38]
	Decreases ethanol consumption (desoxypeganine)	[39]
	Inducing amnesia via interaction with dopaminic receptors (harmane)	[24]
	Modulate voltage-activated calcium- Ica (V)-channels (harmaline and harmane)	[31]
Anti-microbial	Anti-leishmanial activity (harmaline and harmine)	[47]
	Anti-leishmaniasis (visceral) (peganine)	[50]
	Trypanosomicidal activity (via inhibition of respiratory chain) (beta-carbolines) (*Trypanosoma cruzi*)	[53]
	Anti-plasmodial (vasicinone, deoxyvasicinone, and beta-carbolines)	[48]
	Antibacterial	[41]
	Proteus vulgaris and Bacillus subtilis (harmine)	
	Against larvae of *Plodia interpunctella* (hamaline)	[44]
	Inhibition of human DNA Topoisomerase I (harmine, harmane and harmaline)	[61]
Anti-microbial	Intercalation into eukaryotic DNA (harmine>harmalol>harmaline>harmane>tryptoline	[94]
	Inhibition of cyclin dependent kinases (CDKs) (harmaline, harmalol)	[92]
	Activity against: *Streptococcus pyogenus* (l-thioformyl-8- β-D-glucopyranoside-bis-2,3-dihydro- isopyridinopyrrol)	[90]
Endocrine	Emmenaguage and abortive effect (vasicine and vasicinone)	[8]
Gastrointestinal	Blocking different types of intestinal calcium channels (alkaloids specially harmaline)	[71]
Osteocytes	Inhibits osteoclast formation and differentiation	[75,76]
	Enhances osteoblast differentiation (harmine)	
Endocrine	Antidiabetic (regulates the expression of PPARg) (harmine)	[25,80]
P450	Increase expression of CYP1A2, 2C19, and 3A4 whereas decrease the expression of CYP2B6, 2D6 and 2E1 (harmine and harmaline)	[3]
Respiratory	Acts as a bronchodilator (pure vasicine or vasicinone)	[6]

VEGF-NO=Vascular endothelial growth factor-nitric oxide, GABA=Gamma-Aminobutyric acid, Brain-derived neurotrophic factor=Brain-derived neurotrophic factor, MAO-B=Monoamine oxidase B, DNA=Deoxyribonucleic acid, PPARg=Peroxisome proliferator-activated receptor gamma, CYP=Cytochrome P450s

Table 4: Chemical compounds of *P. harmala*

Compound	Type	Part of plant
Harmaline (harmidine)	β-carbolines	Seeds and roots
Harmine (banisterine)		Seeds and roots
Harmalol		Seeds and roots
Harman		Seeds and roots
Tetrahydroharmine		Seeds
Harmol		Seeds
l-thioformyl-8-β-D-glucopyranoside-bis-2,3-dihydroisopyridinopyrrol		Aerial parts
Deoxypeganine	Quinazoline derivatives	Whole plant
Deoxyvasicinone		Seeds
Vasicine (peganine)		Whole plant
Vasicinone		Seeds
Isopeganine		Seeds
Pegamine		Whole plant
Peganol		Whole plant
Peganones		Whole plant
Vascinones		Whole plant
Dipegene		Seeds
9, 14Dihydroxyoctaecanoic-acid		
Ash		
Calcium		
Copper		Whole plant
Dipegene		
Fat		
Fiber		
Protein		
Ruine		
Water		

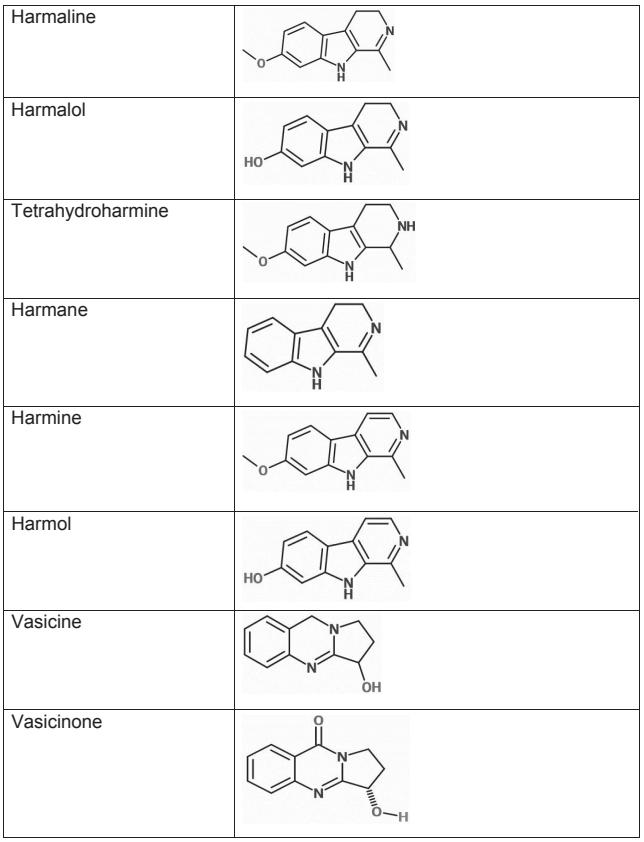

Figure 1: Molecular structure of major alkaloids of *peganum harmala*

Table 5: Toxic doses of various alkaloids of *Peganum harmala*

Alkaloid	Response	Animal	Dose (mg/kg)
Harmaline	LD-sc	Rats	120
Harman	LD-sc	Rabbits	200
Harmine	LD50-iv	Mice	38
Harmine	MLD-sc	Rats	200

LD=Lethal dose, MLD=Median lethal dose

CARDIOVASCULAR EFFECTS

P. harmala is one of the most frequently used medicinal plants to treat hypertension and cardiac disease worldwide.[9,85] It has also been shown in various pharmacological studies that *P. harmala* extract or its main active alkaloids, harmine, harmaline, Harman and harmalol, have different cardiovascular effects such as bradycardia, decreasing systemic arterial blood pressure and total peripheral vascular resistance, increasing pulse pressure, peak aortic flow and cardiac contractile force,[10] Vasorelaxant [11,12] and angiogenic inhibitory effects.[13]

Vasorelaxant and antihypertensive effects

The aqueous (AqE) extract of the seeds of *P. harmala* have antispasmodic, anticholinergic, antihistaminic and antiadrenergic effects.[14] One study on the cardiovascular effects of harmine, harmaline and harmalol indicated that these three alkaloids have vasorelaxant effects with rank order of relaxation potency of harmine >harmaline >harmalol. In case of the first two alkaloids this vasorelaxant activity was not only attributed to their interaction with the alpha 1-adrenergic receptors in vascular smooth muscles but also more importantly to their increasing effect on notric oxide (NO) release from the endothelial cells, which was dependent on the presence of external Ca^{2+}. Harmalol had no effect on the release of NO from the endothelial cells and it weakly interacted with the cardiac 1,4-dihydropyridine binding site of L-type Ca^{2+} channels (Ki value of 408 microM).[11] In the same study, the vasorelaxant activity of harman, another active alkaloid of *P. harmala*, was shown with a mechanism of interaction with the L-type Ca^{2+} channels and increasing NO release from the endothelial cells so dependent on the presence of external Ca^{2+}. These effects of harman may be involved in its hypotensive activity.[15] Another study indicates that the action of harmaline on the prostacyclin pathway also plays a role in its vasoleraxant activity.[12] It has been also shown that harmaline, harmalol and harmine decrease systemic arterial blood pressure and total peripheral vascular resistance obviously not due to activation of cholinergic, beta-adrenergic and histamine (H1) receptors. The harmaline-evoked decreases were frequently followed by a secondary increase and these two effects of harmalol were inconsistent.[10] Astulla *et al.* also showed in

an *in vitro* study the vasorelaxant activity of vasicinone, another alkaloid isolated from the seeds of *P. harmala*, against phenylephrine-induced contraction of isolated rat aorta.[16]

Effects on the heart

There have been a few studies conducted regarding the direct effects of *P. harmala* extract and its alkaloids on heart muscle. For example, in one study it was shown that three *P. harmala* isolated alkaloids (Harmine, Harmaline and Harmalol) have ionotropic effect and also decrease heart rate in normal anesthetized dogs. Since neither vagotomy nor atropinization affected the harmala-induced bradycardia it became evident that the decrease in heart rate was not due to a negative chronotropic effect of the alkaloids.[10]

In another *in vivo* study, harman dose-dependently produced transient hypotension and long-lasting bradycardia in anesthetized rats.[11] Harmaline inhibits both $^{45}Ca^{2+}$ uptake and efflux in cardiac sarcolemal vesicles in a dose-dependent manner.[17]

Angiogenic inhibitory effect

It was revealed in a study that harmine is a potent angiogenic inhibitor. This substance can significantly decrease the proliferation of vascular endothelial cells and reduce expression of different pro-angiogenic factors such as vascular endothelial growth factor, NO and pro-inflammatory cytokines. Nuclear factor-κB and other transcription factors like cAMP response element-binding (CREB) and Activating transcription factor 2 (ATF-2) involved in angiogenesis were also inhibited by harmine. Moreover, harmine decreased production of other factors by tumor cells, which play a significant role in angiogenesis like cyclooxygenase (COX-2), inducible nitric oxide synthase, and matrix metalloproteases.[13]

Inhibitory effect on platelet aggregation

The alkaloids of *P. harmala* are also shown to have anti-platelet aggregation effects.[18] However, there is not so much evidence on this effect of the plant so far.

EFFECTS ON NERVOUS SYSTEM

In traditional medicine, *P. harmala* has been used among societies to treat some nervous system disorders such as Parkinson`s disease,[19] in psychiatric conditions[7] such as nervosity,[20] and to relieve rigorous pain.[21] The alkaloid content of *P. harmala* is shown to be psychoactive[22] and various *in vitro* and *in vivo* studies indicate a wide range of effects produced by *P. harmala* and its active alkaloids on both central and peripheral nervous system including, analgesia,[22,23] hallucination, excitation,[24] and anti-depressant effect.[25,26]

Some of these alkaloids such as harmaline, harmine, and norharmane are also endogenous compounds present in the body and since they have been found in high plasma concentrations in alcoholics,[27] drug addicts,[28] smokers,[29] and patients with Parkinson`s disease,[30] they are thought to be crucially involved in various central nervous system (CNS) problems.

It has been also proven that *P. harmala*-derived beta-carbolines interact with opioid,[21] dopamine,[24] GABA (Gamma-Aminobutyric acid),[31] 5-hydroxytryptamine, benzodiazepine, and imidazoline[32] receptors present in the nervous system and this way induce their many pharmacological effects. Moreover, these alkaloids are neuroprotective [31,33] and strong inhibitors of monoamine oxidase and this important feature makes them a preferable target in the treatment of some conditions like depression.[25]

Mono amine oxidase inhibition and anti-depressant effect

Beta-carbolines present in *P. harmala* strongly inhibit monoamine oxidase enzyme that is the main factor in degradation and reuptake of monoamines like serotonin and norepinephrine. It was pointed out in an *in vitro* study that seed and root extracts of *P. harmala* significantly inhibits MAO-A but has no effect on MAO-B. In case of the seed extract the inhibitory effect was reversible and competitive with an IC_{50} of 27 μg/l and it was mostly attributed to harmaline and harmine. The strong inhibitory effect of the root extract was only due to harmine and the IC_{50} was calculated as159 μg/l.[7] It could be concluded that this inhibitory effect has the potential to reverse the MAO-mediated monoamine reduction in depression. Harmine at high doses increased the BDNF (Brain-derived neurotrophic factor) protein level, which is decreased in depressive conditions, while imipramine, a common anti-depression drug, had no such effect.[25] Farzin *et al*. revealed in a study on the anti-depressant effects of harmane, norharmane, and harmine using the mouse force swim test that these alkaloids of *P. harmala* have a significant dose-dependent anti-depressive effect with a suggested mechanism of acting on benzodiazepine receptors. It was shown in another *in vitro* study that the extract of *P. harmala* has the ability to inhibit catechol-O-methyltransferase and thereby the methylation of catecholamines with a mixed type mechanism.[34] All of these effects represent an idea that *P. harmala* and its derivatives could be used for treatment of mood disorders and are potent alternatives for current anti-depression drugs.

Analgesic and antinociceptive effects

The analgesic effect of different forms of *P. harmala* extract (ethyl acetate [EAE], butanolic [BE], and AqE) have been investigated in various parallel studies. The methods used in these studies include formalin, hot plate, and writhing tests. The results showed that all forms of the extracts produced the analgesic effect. Among the

extracts, BE showed the maximum effect with a percentage of 35.12% in the writhing test. In case of the AqE, the nociceptive effect was only observed in the second phase of the formalin test. Treatment with both EAE and BE produced a dose-dependent analgesia. Since treatment with naloxone prevented the nociceptive effect of the extracts, it is concluded that an opioid-modulated mechanism is involved. The results also indicated that the extracts act both centrally and peripherally.[21,23,35]

Relation with Parkinson's disease

The endogenous harmala alkaloids have been proven to be involved in Parkinson's disease.[31] One study on both endogenous and exogenous beta-carbolines showed that they all have general DAT-mediated (Dopamine active transporter-mediated) dopaminergic toxicity and therefore, are involved in the pathogenesis of Parkinson's disease.[36] Adversely, it was revealed in an *in vitro* study that two of these endogenous compounds, norharman and 9-methylnorharman, have good anti-parkinsonism effects via inhibition of MAO-B, an enzyme involved in the production of parkinsonism-related substances from the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. However, naturally occurring beta-carbolines had almost no such inhibitory effect.[33]

In contrast, several studies on the anti-parkinsonism effect of *B. caapi* revealed that its beta-carboline content (harmine and harmaline) has significant effect against this disease through the inhibition of MAO-B.[37,38] Although, these beta-carbolines with anti-parkinsonism effect are also present in *P. harmala*, there have been no studies conducted regarding the possible effect of *P. harmala* isolated alkaloids against Parkinson's disease, thus far.

Other neuropsychological effects

There have been reports of other effects produced by *P. harmala* in the nervous system.

In an *in vitro* study desoxypeganine, one of the *P. harmala* alkaloids, dose-dependently decreased ethanol consumption in female Alko alcohol rats with no effect on food and fluid consumption.[39] This may represent a safe way to decrease the consumption of alcohol in alcoholics. Harmane, another alkaloid isolated from *P. harmala* induced amnesia with a suggested mechanism of interaction with dopaminic (D_1 and D_2) receptors.[24] Harmaline and harmane have been shown to modulate voltage-activated calcium- $I_{Ca(V)}$-channels *in vitro* and in a reversible and use independent manner.[31]

ANTIMICROBIAL EFFECTS

Various studies have shown different antiparasidal,[16,40] antifungal,[41,42] antibacterial[41,43] and insecticidal[44,45] effects of the alkaloids derived from *P. harmala* seeds. It has also been used widely as an anti-fungal[42] and antiparasidal[46] agent in traditional medicine of some parts of the world. For instance, in Saudi Arabia it has been so common to use *P. harmala* against fungal infections.[42] In one study, the methanolic, AqE and chloroform extracts of *P. harmala* were shown to have respectively strong, moderate, and slight inhibitory effects on the growth of *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger* and *Candida albicans*.[42]

Preparations of *P. harmala* were also used in folk medicine of South-Eastern Spain as anti-leishmanial remedies.[46] Moreover, its powdered seeds and various extracts have been used as a remedy against tapeworm infections in men and animals in the indigenous system of medicine.[40]

Antiprotozoal effect

Various studies have been carried out investigating *in vitro* and *in vivo* effects of different *P. harmala* extracts on forms of leishmania parasites. One study on the effect of *P. harmala* extract on *Leishmania infantum* revealed that harmine and harmaline have weak anti-leishmanial activity against both promastigote and amastigote form of the parasite. At the same time, harmaline showed strong toxicity against the amastigote forms inside the macrophages. The suggested mechanism for this property is the inhibitory effect of harmaline on protein kinase C (PKC) action of the parasites.[47] Another study compared the *in vitro* antileishmanial activity of antimonyl tartrate and *P. harmala* extract against L. major. During this study the extract showed the same potency as antimonyl tartrate that means it could be a good alternative for the antimonial drugs as the first-line antileishmanial treatments with lots of severe side effects.[48] The effectiveness of the extract is mostly attributed to its beta-carboline content. *P. harmala* extract also decreased the lesion size and number of the parasites in cutaneous form of the disease.[49] In addition to the beta-carbolines, peganine another alkaloid of *P. harmala*, was shown to have strong *in vitro* and *in vivo* toxicity against both amastigotes and promastigotes of *Leishmania donovani*. A dose of 100 mg/kg body weight of peganine was effective against visceral leishmaniasis in hamsters.[50]

There have been several studies indicating effectiveness of *P. harmala* extract against theileriosis.[51,52] Two studies were conducted in Iran on the effect of *P. harmala* extract with a dose of 5mg/kg body weight once daily for 5 days on cattle[52] and sheep[51] theileriosis that showed a significant recovery rate of respectively 78% and 65%.

Beta-carbolines from the seeds of *P. harmala* showed strong trypanosomicidal activity against nifurtimux-resistant LQ strain of *Trypanosoma cruzi*. Inhibition of respiratory chain appears to be the possible determinant of this action of beta-carbolines.[53]

Furthermore, there have been reports of antiplasmodial activity of different *P. harmala* alkaloids such as vasicinone, deoxyvasicinone, and beta-carbolines.

Antibacterial activity

One of other important features of *P. harmala* alkaloids is their bactericidal activity that is comparable with that of common antibiotics, which have many adverse effects. Different species of bacteria have been shown to be susceptible to these alkaloids. For example *Proteus vulgaris and Bacillus subtilis* appeared to be very sensitive to harmine.[41] The activity of these alkaloids depended on the microorganism and the application method. For instance, the methanolic extract showed higher antibacterial potency against all tested micro-organisms (*Staphylococcus aureus, Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae,* and *P. vulgaris*) than other chloroform and petroleum extracts in one study.[43]

It is concluded that *P. harmala* and its alkaloids could probably be used for the control of antibiotic resistant isolates of bacteria.[54]

Insecticidal and antifungal activity

In vitro treatment with individual alkaloids of *P. harmala* or a mixture of them was so efficient against *A. niger* and *C. albicans* with a minimal inhibitory concentration of total (crude) alkaloids respectively 0.333 ± 0.007 MIC (Minimum inhibitory concentration) (mg/ml) and 0.333 ± 0.007 MIC (mg/ml).[41] A synergistic activity of different alkaloids present in the crude extract might be involved in its strong effect.

Furthermore, there have been some reports about insecticidal activity of *P. harmala*-derived beta-carbolines indicating their inhibitory effects on the development and growth of the larval stages of some insects. For example harmaline prevented the development of larvae of *Plodia interpunctella,* an insect pest of stored food, to the pupal and adult stages.[44] This inhibitory effect of harmaline was due to its severe toxicity on the epithelial cells of the midgut that finally leads to shedding of the cytoplasm contents into the midgut lumen.

Another study showed the insecticidal activity of methanolic *P. harmala* extract against *Tribolium castaneum,* the stored grain pest. Larvae growth was significantly inhibited with the incorporation of the extract into their diet. The adult form of the insect was also susceptible. It could be a good idea to use *P. harmala* as a tool to control the population of such harmful insects.[45]

Antineoplasm, antiproliferative and antioxidant effects

Since ancient times, *P. harmala* has been used by traditional healers to make various preparations in the treatment of cancers and tumors in some parts of the world. [13,55] For example, it has been so common in traditional medicine of Morocco to use powdered seeds of *P. harmala* to treat skin and subcutaneous tumors.[56] The seed extract of *P. harmala* is the main component of a very common ethnobotanical preparation used against different cancers and neoplasms in Iran, namely Spinal-Z.[57,58]

The antitumor activity of *P. harmala* and its active alkaloids (mainly beta-carbolines) have also drawn attentions of many researchers worldwide that has led to various pharmacological studies regarding this important effect of *P. harmala.* [23,56] Various authors have reported cytotoxicity of *P. harmala* on tumor cell lines *in vitro* and *in vivo*. In one study, the methanolic extract of *P. harmala* reduced significantly proliferation of three tested tumor cell lines (UCP-Med (a tumor cell line), Med-mek carcinoma, and UCP-Med sarcoma) in all concentrations. This anti-proliferative effect was produced by the alkaloid fraction of the extract in the first 24 h of the treatment. A cell lysis effect was observed in the next 24 h and thus, resulted in complete cell death within 48 to 72 h.[56] The same results were observed with the total extract of the plant in another study. The extract also showed cytotoxicity against artificially grafted subcutaneous Sp2/O cell-line in BALB-c (Albino) mice.[56] Administration of different beta-carboline alkaloids isolated from *P. harmala* showed inhibitory effect against Lewis Lung cancer sarcoma-180 or HepA tumor in mice at rates of 15.3-49.5%. Substitution of formate at R_3 and aryl at R_9 of the tricyclic skeleton respectively decreased neurotoxicity and increased the inhibitory effects of the alkaloids that made them ideal agents to be used as novel antitumor drugs with lesser side effects.[55] Several *in vitro* and *in vivo* studies have revealed that these cytotoxicity and antitumor effects of *P. harmala* are related to its interaction with RNA,[59] DNA and its synthesis, [56,60] and inhibition of human Topoisomerase.[58] In a study conducted in Iran, it was shown using the DNA relaxation assay that the extract of *P. harmala* inhibits human DNA Topoisomerase I. This effect was attributed to the beta-carboline content of the extract and potency of the alkaloids were determined as harmine >harmane >harmaline in a way that treatment with the total extract showed weaker inhibitory effect than treatment with every individual alkaloid.[58] Another study indicated that harmine and its derivatives have inhibitory effect on human Topoisomerase I activity but no effect on Topoisomerase II. Intercalation of several carbolines into eukaryotic DNA has also been reported by many authors. [58,61] This intraction of beta-carbolines cause significant structural changes in DNA and interfere with its synthesis.[56,61] The alkaloid-DNA binding affinity was ordered as harmine >harmalol >harmaline >harmane >tryptoline. There are also other suggested mechanisms for the anti-tumor activity of *P. harmala* alkaloids. In an *in vitro* study by Li *et al*., budding yeast was used as a model to

investigate the anti-tumor activity of *P. harmala*. Results showed that DH334, a beta-carboline derivative and an anticancer drug, specifically inhibits cyclin dependent kinases (CDKs) and blocks the initiation of cell cycle at the G_1 phase. It also inhibited the kinase activity of Cdk2/CyclinA (a member of the cyclin family) *in vitro*. This could be another possible mechanism for the antitumor activity of the drug.[56,93]

Many pharmacological studies suggest an antioxidant and free radical scavenging effect of *P. harmala*. This effect has been attributed to the increasing effect of *P. harmala* extract on E_2 (17β-estradiol) level as an important antioxidant and reactive oxygen species (ROS) scavenger.[12,62,63] In another study, the effects of harmaline and harmalol were tested on Digoxin-induced cytochrome P450 1A1 (CYP1A1), a carcinogen-activating enzyme, in human hepatoma HepG2 cells. These alkaloids significantly inhibited the enzyme via both transcriptional and posttranslational mechanisms in a concentration-dependent manner.[3] Ethanol and chloroform extracts of *P. harmala* showed protective effects against thiourea-induced carcinogenicity by normalization of neuron-specific enolase and thyroglobulin levels in animal models.[64] Other effects of the plant extract such as anti-proliferative effect on Leukemic cell lines,[65] inhibitory action on the metastasis of melanoma cells, inducing apoptosis in melanoma cells,[66] tumor angiogenesis inhibition,[13] and binding to RNA[61] have also been reported by various authors. In some cases, *P. harmala* showed a higher selectivity towards malignant cells than common anticancer drugs like doxorubicin.[57] All of these data suggest that *P. harmala* and its alkaloids possess the potential to be used as novel antioxidant and anti-tumor agents in anti-cancer therapy.

INDUCING EMMENAGOGUE AND ABORTION

P. harmala has been used traditionally as an effective emmenagogue and abortificient agent in the Middle East, India, and North Africa.[6,56,67] It has also been shown that abortion happens frequently among animals that digest this plant in a dry year.[8,68] Quinazoline alkaloids (e.g., vasicine and vasicinone) within *P. harmala* have been attributed to the abortificient effect of this plant.[8]

GASTROINTESTINAL EFFECTS

P. harmala extract and powdered seeds have been used in folk medicine of different parts of the world to treat colic in man and animals.[40] The efficiency of this plant in treatment of colic is due to its antispasmodic effect[69] probably as a result of blocking different types of intestinal calcium channels[70] by the alkaloid content of the plant specially harmaline. *P. harmala* also possesses noticeable nauseant[71] and emetic [7,72] effects.

OSTEOGENIC ACTIVITY

Two different studies conducted by Yonezawa *et al.* showed bone anabolic effects of harmine, *in vivo* and *in vitro*.[73,74] It was revealed that administration of 10 mg/kg/day of harmine inhibits formation and differentiation of osteoclasts in mice via down-regulation of c-Fos (A cellular proto-oncogene) and NFATc1 (Nuclear factor of activated T-cells, cytoplasmic 1) and thus, prevents osteoclast-mediated resorption. Adversly, it enhances osteoblast differentiation probably via inducing the expression of BMPs and activation of bone morphogenetic protein (BMP) and Runx2 pathways. It was also found that carbon C_3C_4 double-bond and 7-methoxy group of harmine plays an important role in these processes. These findings suggest that harmine, as the main alkaloid of *P. harmala*, may be useful for treatment of some bone diseases.

IMMUNE SYSTEM EFFECTS

Beta-carboline alkaloids of *P. harmala* are shown to have immune-modulatory effects in several studies.[26,75] Extracts of this plant have significant anti-inflammatory effect via the inhibition of some inflammatory mediators including prostaglandin E_2 (PGE_2) (100 μg/mg) and tumor necrosis factor alpha (TNF-α) (10 μg/mg).[46]

ANTIDIABETIC EFFECTS

P. harmala has been traditionally used to treat diabetes in folk medicine of some parts of the world.[69,76] This effect of *P. harmala* has been pharmacologically confirmed in several studies one of which showed that the plant would lose its hypoglycemic activity at high doses instead of increasing it.[77] Harmine is the main alkaloid of *P. harmala* that is involved in its anti-diabetic effect.[25] One study shows that harmine regulates the expression of peroxisome proliferator-activated receptor gamma (PPARγ), the main regulator of adipogenesis and the molecular target of the thiazolidinedione antidiabetic drugs, through inhibition of the Wnt signaling pathway. Therefore, it mimics the effects of PPARg ligands on adipocyte gene expression and insulin sensitivity without showing the side-effects of thiazolidinedione drugs such as weight gain.[78]

TOXICITY

In addition to all therapeutic effects of *P. harmala*, there have been several reports of human[79] and animal[68] intoxications induced by this plant. There are also experimental studies indicating *P. harmala* toxicity. [6,7] In an *in vitro* study, intrapretoneal administration of three different extracts of *P. harmala* at a dose of 50 mg/kg body weight induced

sympthoms such as: Abdominal writhing, body tremors and slight decrease in locomotor activity,[21] while oral administration of these extracts showed no toxicity. There have been also the same symptoms reported in different human cases[2,6,80] following ingestions of *P. haramala* seed extract or infusion including: Neuro-sensorial symptoms, visual hallucination, slight elevation of body temperature, cardio-vascular disorder such as bradycardia and low blood pressure, psychomotor agitation, diffuse tremors, ataxia and vomiting. Despite animal intoxications in almost all of human cases, *P. harmala* poisonings were relieved in a few hours.[6] *P. harmala* extract is toxic at high-doses[7,77,81,82] and can cause paralysis, liver degeneration, spongiform changes in the central nervous system,[83] euphoria, convulsions, digestive problems (nausea, vomiting), hypothermia and bradycardia.[2,6,68,80] However, therapeutic doses have been reported to be safe in a rodent model.[54]

MAO inhibition activity of *P. harmala* components are the main cause for the toxicological effects after ingestion of the plant.[7] Moreover, the intercalation of *P. harmala* alkaloids into DNA has led to its mutagenic property which causes genotoxic effects.[84] *P. harmala* methanolic extract has showed teratogenic effects in female rats.[68] The extract prolonged diestrus phase, reduced number of living pups, and decreased the number of resorption. It also dose-dependantly decreased litter size.[8] These data all together suggest that care should be taken while using *P. harmala* and its derivatives as therapeutic agents in order to prevent probable intoxications.

DRUG INTERACTION

P. harmala is shown to interact with drug metabolism due to its significant effects on the expression of cytochrome P450s (CYP), the most important superfamily of drug metabolizing enzymes. Seeds of this plant dose-dependently increase the expression of CYP1A2, 2C19, and 3A4 whereas decrease the expression of CYP2B6, 2D6 and 2E1. Harmine and harmaline are the main contents involved. These data all together suggest that care should be taken when *P. harmala* is co-administered with other drugs.[3]

CONCLUSION

Our aim in preparing this paper was to show the traditional usage and previously confirmed pharmacological effects of *P. harmala* as one of the most well-known medicinal plants in Iran and to illustrate it's potential to be used as a novel source for the development of new drugs based on the most recent associated studies. As it is evident from this study, *P. harmala* has a wide range of pharmacological effects including cardiovascular, nervous system, gastrointestinal, antimicrobial, antidiabetic, osteogenic, immunomodulatory, emmenagogue, and antitumor activity among many other effects. Beta-carboline alkaloids contained in *P. harmala* are the most important contents of the plant responsible for most of its pharmacological effects. Since there have been many reports of intoxications following ingestion of specific amounts of *P. harmala* seeds, care should be taken by scientists and clinicians regarding usage of this plant for therapeutic purposes until adequate studies confirm the safety and quality of the plant. Finally, based on this information, this review provides the evidence for other researchers to introduce *P. harmala* as a safe and effective therapeutic source in the future.

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