Review Article ISSN: 2349-2678

Contents lists available at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

NLM (National Library of Medicine ID: 101738825)

Index Copernicus Value 2019: 71.05

Volume 10 Issue 4; July-August; 2022; Page No. 14-20

A Review on *Peganum Haramal* (Nitrariaceae): Traditional uses, Phytochemistry and Pharmacological Properties

Jahiruddin[1], Rakesh Sharma[2], Surbhi Jangir[2]

[1]Research Scholar, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

[2]Associate Professor, Department of Pharmacology, Jaipur College of Pharmacy, Jaipur, Rajasthan, India

Conflicts of Interest: Nil

Corresponding author: Jahiruddin

ABSTRACT

Peganum harmal, commonly called wild rue, Syrian rue, African rue, esfand or spand, or harmel. It is a perennial, herbaceous plant, with a woody underground root-stock, of the family Nitrariaceae, usually growing in saline soils in temperate desert and Mediterranean regions. It has become an invasive species in some regions of the western United States. The plant is popular in Middle Eastern and North African folk medicine. Harmala demonstrated numerous medicinal effects including cardiovascular, neurologic, antimicrobial, insecticidal, antineoplasmic, antiproliferative, gastrointestinal and antidiabetic effects. Phytochemical investigations have indicated the existence of a number of active alkaloids in P. harmala, especially beta-carbolines such as harmalol, harmaline, and harmine. Harmala demonstrated numerous medicinal effects including cardiovascular, neurologic, antimicrobial, insecticidal, antineoplasmic, antiproliferative, gastrointestinal and antidiabetic effects.

Keywords: Peganum harmal, Mediterranean regions, invasive species, phytochemical investigation

Introduction

Peganum harmala

Peganum harmal, commonly called wild rue, Syrian rue, African rue, esfand or spand, or harmel (among other similar pronunciations and spellings). Peganum haramala is a perennial, herbaceous plant, with a woody underground root-stock, of the family Nitrariaceae, usually growing in saline soils in temperate desert and Mediterranean regions. Its common English-language name came about because of a resemblance to rue (to which it is not related). Because eating it can cause livestock to sicken or die, it is considered a noxious weed in a number of countries. It has become an invasive species in some regions of the western United States. The plant is popular in Middle Eastern and North African folk medicine. The alkaloids contained in the plant, including the seeds, are monoamine oxidase inhibitors (Harmine, Harmaline).

Scientific Classification

Kingdom	:	Plantae
Clade	:	Tracheophytes
Clade	:	Angiosperms
Clade	:	Eudicots
Clade	:	Rosids
Order	:	Sapindales
Family	:	Nitrariaceae
Genus	:	*Peganum*
Species	:	*P. harmala*
Binomial name	:	Peganum harmala

Habitate

It is a perennial, herbaceous, suffrutescent, hemicryptophyte plant, which dies off in the winter, but regrows from the rootstock the following spring. It can grow to about 0.8 m (3 ft) tall, but normally it is about 0.3 m (1 ft) tall. The entire plant is hairless (glabrous). Plants bad taste and smell foul when crushed.

Stems

Numerous erect to spreading stems grow from the crown of the root-stock in the spring, these branch in a corymbose fashion.

Roots

The roots of the plant can reach a depth of up to 6.1 m (20 ft), if the soil where it is growing is very dry. The roots can grow to 2 cm (0.8 in) thick.

Seeds

The seeds are alternate, sessile, and have bristly, 1.5–2.5 mm (0.06–0.10 in) long stipules at the base. The seed blade is dissected/forked twice or more into three to five thin, linear to lanceolate-linear, greyish lobes. The forks are irregular. The lobes have smooth margins, are 3–5 cm (1.2–2.0 in) long and 1–5 mm (0.04–0.20 in) broad, and end in points.

Medicinal Uses

Harmala demonstrated numerous medicinal effects including cardiovascular, neurologic, antimicrobial, insecticidal, antineoplasmic, antiproliferative, gastrointestinal and antidiabetic effects.

Chemical Constituents

Phytochemical investigations have indicated the existence of a number of active alkaloids in P. harmala, especially beta-carbolines such as harmalol, harmaline, and harmine. Methanol extract of P. harmala seed has a high phenolic content and high antioxidant activity. Its psychopharmacological and toxicological properties are attributed to quinazoline and β-carboline alkaloids. Quinazoline alkaloids are able to have bronchodilator and abortifacient actions, and could contribute to the impacts reported in P. harmala. The β-Carboline alkaloids have an expansive pharmacological range of antimicrobial and antiviral agents. The harmane and flazinamide in βC have anti-HIV activity. Moreover, several derivatives of 1,3-disubstituted βC that have a substituted carbohydrazide group at C-3 will be active against vaccinal poliovirus and HSV-1. Furthermore, 9-methylharmine inhibited dengue virus 2 in vitro. Also, a study conducted on the antiviral activity of harmine, a photoactive β-carboline alkaloid, revealed that harmine + UVA will be able to inactivate protein and RNA synthesis and DNA replication in cytomegalovirus.

Literature review on basis of pharmacological activities

Cardioprotective Activity

- Berrougui H, ***et al*** **(2006)** investigated Vasorelaxant effects of harmine and harmaline extracted from *Peganum harmala* L. seeds in isolated rat aorta[1].

- Shi CC, ***et al*** **(2001)** investigated Comparative study on the vasorelaxant effects of three harmala alkaloids *in vitro*[2].
- Aarons DH, ***et al*** **(1977)** investigated cardiovascular actions of three harmala alkaloids: Harmine, harmaline, and harmalol[3].

Anticancer Activity

- Hamsa TP, ***et al*** **(2011)** investigated Harmine activates intrinsic and extrinsic pathways of apoptosis in B16F-10 melanoma[4].
- Hamsa TP, ***et al*** **(2010)** investigated Harmine inhibits tumour specific neo-vessel formation by regulating VEGF, MMP, TIMP and proinflammatory mediators both *in vivo* and *in vitro*[5].
- Zaker F, ***et al*** **(2007)** investigated a study on the antitumoral and differentiation effects of *Peganum harmala* derivatives in combination with ATRA on leukaemic cells. Arch[6].
- Zaker F, ***et al*** **(2007)** investigated a study on the antitumoral and differentiation effects of *peganum harmala* derivatives in combination with ATRA on leukaemic cells[7].
- Mirzaei M. **(2007)** investigated treatment of natural tropical theileriosis with the extract of the plant *Peganum harmala*[8].
- Mirzaie dehaghi M. **(2006)** investigated treatment of natural ovine malignant theileriosis with a chloroform extract of the plant *Peganum harmala*[9].
- Chen Q, ***et al*** **(2005)** investigated antitumor and neurotoxic effects of novel harmine derivatives and structure-activity relationship analysis[10].
- Lamchouri F, ***et al*** **(2000)** investigated *in vitro* cell toxicity of *Peganum harmala* alkaloids on cancerous cell lines[11].
- Wang X, ***et al*** **(1996)** investigated study on the antitumor effect of total harmala[12].
- Ishida J, ***et al*** **(1999)** investigated anti-tumor agents (201) cytotoxicity of Harmine and Bcarboline analogs[13].
- Lamchouri F, ***et al*** **(1999)** investigated antitumour principles from *Peganum harmala* seeds[14].

Antispasmodic Activity

- Aqel M, ***et al*** **(1991)** investigated direct relaxant effect of *Peganum harmala* seed extract on smooth muscles of rabbit and guinea pig[15].

Antimalarial Activity

- Astulla A, ***et al*** **(2008)** investigated Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities[16].

Analgesic Activity

- Farouk L, ***et al*** **(2008)** investigated evaluation of the analgesic effect of alkaloid extract of *Peganum harmala* L.: Possible mechanisms involved[17].
- Monsef HR, ***et al*** **(2004)** investigated antinociceptive effects of *Peganum harmala* L. alkaloid extract on mouse formalin test[18].

Psychotropic Activity

- Nasehi M, ***et al*** **(2010)** investigated involvement of dopamine D1/D2 receptors on harmane-induced amnesia in the step-down passive avoidance test[19].

Antidepressant Activity

- Fortunato JJ, ***et al*** **(2009)** investigated acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus[20].
- Farzin D, and Mansouri N **(2006)** investigated antidepressant-like effect of harmane and other beta-carbolines in the mouse forced swim test[21].

Antibacterial Activity

- Nenaah G. **(2010)** investigated antibacterial and antifungal activities of (beta)-carboline alkaloids of *Peganum harmala* (L) seeds and their combination effects[22].
- Darabpour E, ***et al*** **(2010)** investigated Antibacterial activity of different parts of *Peganum harmala* L. growing in Iran against multi-drug resistant bacteria[23].
- Minan YH **(2010)** investigated Antimicrobial Effects of Aqueous and Alcoholic Extract of *Peganum Harmala* L. Seeds[24].

- Arshad N, ***et al*** **(2008)** investigated Effect of *Peganum harmala* or its beta-carboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry[25].
- Prashanth D, and John S. **(1999)** investigated Antibacterial activity of *Peganum harmala*[26].

Insecticidal Activity

- Rharrabe K, ***et al*** **(2007)** investigated Bioinsecticidal effect of harmaline on *Plodia interpunctella* development (*Lepidoptera Pyralidae*)[27].

Antileishmanial Activity

- Rahimi-Moghaddam P, ***et al*** **(2011)** investigated i*n vitro* and *in vivo* activities of *Peganum harmala* extract against *Leishmania major*[28].
- Khaliq T, ***et al*** **(2009)** investigated peganine hydrochloride dihydrate an orally active antileishmanial agent[29].
- Jiménez J, ***et al*** **(2008)** investigated cytotoxicity of the beta-carboline alkaloids harmine and harmaline in human cell assays *in vitro*[30].
- Mirzaie M, ***et al*** **(2007)** investigated antileishmanial activity of *Peganum harmala* extract on the in vitro growth of Leishmania major promastigotes in comparison to a trivalent antimony drug[31].
- Mirzaie M, ***et al*** **(2007)** investigated antileishmanial activity of *Peganum harmala* extract on the *in vitro* growth of *Leishmania major* promastigotes in comparison to a trivalent antimony drug[32].
- Di Giorgio C, ***et al*** **(2004)** investigated i*n vitro* activity of the beta-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species *Leishmania infantum*[33].
- Sobhani AM, ***et al*** **(2002)** investigated an *in vitro* evaluation of human DNA topoisomerase I inhibition by *Peganum harmala* L. seeds extract and its beta-carboline alkaloids[34].

Antidiabetic Activity

- Nafisi S, ***et al*** **(2011)** investigated possible antidiabetic effect of *Peganum harmala* on streptozocine-induced mouse[35].
- Singh AB, ***et al*** **(2008)** investigated preliminary studied on the hypoglycemic effect of *Peganum harmala* seeds ethanol extract on normal and streptozocine induced diabetic rats[36].
- Waki H, ***et al*** **(2007)** investigated the small molecule harmine is an antidiabetic cell-type-specific regulator of PPAR gamma expression[37].

Abortifacient Activity

- Shapira Z, ***et al*** **(1989)** investigated abortifacient potential for the epigeal parts of *Peganum harmala*[38].

Anti-fungal Activity

- Diba K, ***et al*** **(2011)** investigated anti-fungal activity of alcoholic extract of *Peganum harmala* seeds[39].

Antiviral Activity

- Kiani SJ, ***et al*** **(2008)** investigated p*eganum harmala* seed extract can prevent HSV-1 replication *in vitro*[40].
- Kujumgiev A, ***et al*** **(1999)** investigated antibacterial, antifungal and antiviral activity of propolis of different geographic origin[41].

Anti-protozoal Activity

- Phillipson JD, ***et al*** **(1987)** investigated new leads to the treatment of protozoal infections based on natural product molecules[42].

Conclusion

It is seen from the literature that *Peganum harmala* is a very important plant for its large number of medicinal properties as well as medicinally important chemicals especially beta-carbolines such as harmalol, harmaline, and harmine. Its psychopharmacological and toxicological properties are attributed to quinazoline and β-carboline alkaloids. Harmala demonstrated numerous medicinal effects including cardiovascular, neurologic, antimicrobial, insecticidal, antineoplasmic, antiproliferative, gastrointestinal and antidiabetic effects. Many pharmacological activities are like wound healing, anti-

inflammatory, anti-oxidant, anti-viral, antiprotozoal, anti-fungal activity, abortifacient activity, antidiabetic activity and antileishmanial activity which are being studied till today. Thus, as folk medicine *Peganum harmala* has many uses as a multipurpose medicinal agent so further clinical trials should be performed to prove its efficacy. Because of their wide utilization, the plant deserves special research attention of these uses and compounds.

References

1. Berrougui H, Martín-Cordero C, Khalil A, Hmamouchi M, Ettaib A, Marhuenda E, *et al*. Vasorelaxant effects of harmine and harmaline extracted from *Peganum harmala* L. seeds in isolated rat aorta. Pharmacol Res 2006;54:150-7.
2. Shi CC, Liao JF, Chen CF. Comparative study on the vasorelaxant effects of three harmala alkaloids *in vitro*. Jpn J Pharmacol 2001;85:299-305.
3. Aarons DH, Rossi GV, Orzechowski RF. Cardiovascular actions of three harmala alkaloids: Harmine, harmaline, and harmalol.J Pharm Sci 1977;66:1244-8.
4. Hamsa TP, Kuttan G. Harmine activates intrinsic and extrinsic pathways of apoptosis in B16F-10 melanoma. Chin Med 2011;6:11.
5. Hamsa TP, Kuttan G. Harmine inhibits tumour specific neo-vessel formation by regulating VEGF, MMP, TIMP and pro-inflammatory mediators both *in vivo* and *in vitro*. Eur J Pharmacol 2010;649:64-73.
6. Zaker F, Oody A, Arjmand A (2007). A study on the antitumoral and differentiation effects of *Peganum harmala* derivatives in combination with ATRA on leukaemic cells. Arch. Pharm. Res., 30(7): 844-849.
7. Zaker F, Oody A, Arjmand A. A study on the antitumoral and differentiation effects of *peganum harmala* derivatives in combination with ATRA on leukaemic cells. Arch Pharm Res 2007;30:844-9.
8. Mirzaei M. Treatment of natural tropical theileriosis with the extract of the plant *Peganum harmala*. Korean J Parasitol 2007;45:267-71.
9. Mirzaiedehaghi M. Treatment of natural ovine malignant theileriosis with a chloroform extract of the plant *Peganum harmala*. Onderstepoort J Vet Res 2006;73:153-5.
10. Chen Q, Chao R, Chen H, Hou X, Yan H, Zhou S, *et al*. Antitumor and neurotoxic effects of novel harmine derivatives and structure-activity relationship analysis. Int J Cancer 2005;114:675-82.
11. Lamchouri F, Settaf A, Cherrah Y, Hasser M, Zemzami M, Arif N, Nadori EB, Zaid A, Lyoussi B (2000). *In vitro* cell toxicity of *Peganum harmala* alkaloids on cancerous cell lines. Fitoterapia, 71: 50-54.
12. Wang X, Wang H, He A. Study on the antitumor effect of total harmala. J China Med Univ 1996;25:240-2.
13. Ishida J, Wang HK, Bastow KF, Hu CQ, Lee KH (1999). Anti tumor agents (201) cytotoxicity of Harmine and Bcarboline analogs. Bioorg. Med. Chem. Lett., 9: 3319-3324.
14. Lamchouri F, Settaf A, Cherrah Y, Zemzami M, Lyoussi B, Zaid A, *et al*. Antitumour principles from *Peganum harmala* seeds. Therapie 1999;54:753-8.
15. Aqel M, Hadidi M. Direct relaxant effect of *Peganum harmala* seed extract on smooth muscles of rabbit and guinea pig. Pharm Biol 1991;29:176-82.
16. Astulla A, Zaima K, Matsuno Y, Hirasawa Y, Ekasari W, Widyawaruyanti A, *et al*. Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities.J Nat Med 2008;62:470-2.
17. Farouk L, Laroubi A, Aboufatima R, Benharref A, Chait A. Evaluation of the analgesic effect of alkaloid extract of *Peganum harmala* L.: Possible mechanisms involved. J Ethnopharmacol 2008;115:449-54.
18. Monsef HR, Ghobadi A, Iranshahi M, Abdollahi M. Antinociceptive effects of *Peganum harmala* L. alkaloid extract on mouse formalin test. J Pharm Pharm Sci 2004;7:65-9.
19. Nasehi M, Piri M, Nouri M, Farzin D, Nayer-Nouri T, Zarrindast MR.

Involvement of dopamine D1/D2 receptors on harmane-induced amnesia in the step-down passive avoidance test. Eur J Pharmacol 2010;634:77-83.
20. Fortunato JJ, Réus GZ, Kirsch TR, Stringari RB, Stertz L, Kapczinski F, *et al*. Acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:1425-30.
21. Farzin D, Mansouri N. Antidepressant-like effect of harmane and other beta-carbolines in the mouse forced swim test. Eur Neuropsychopharmacol 2006;16:324-8.
22. Nenaah G. Antibacterial and antifungal activities of (beta)-carboline alkaloids of *Peganum harmala* (L) seeds and their combination effects. Fitoterapia 2010;81:779-82.
23. Darabpour E, Poshtkouhian Bavi A, Motamedi H, Seyyed Nejad SM (2011). Antibacterial activity of different parts of *Peganum harmala* L. growing in Iran against multi-drug resistant bacteria. Excl. J., 10: 252-263.
24. Minan YH (2010). Antimicrobial Effects of Aqueous and Alcoholic Extract of *Peganum Harmala* L. Seeds on Two Types of Salivary Isolated Microorganisms in Al-Ramadi City. Pharmacol. JKAU Med. Sci., 17(4): 3-17.
25. Arshad N, Zitterl-Eglseer K, Hasnain S, Hess M. Effect of *Peganum harmala* or its beta-carboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry. Phytother Res 2008;22:1533-8.
26. Prashanth D, John S. Antibacterial activity of *Peganum harmala*. Fitoterapia 1999;70:438-9.
27. Rharrabe K, Bakrim A, Ghailani N, Sayah F. Bioinsecticidal effect of harmaline on *Plodia interpunctella* development (*Lepidoptera Pyralidae*). Pestic Biochem Physiol 2007;89:137-45.
28. Rahimi-Moghaddam P, Ebrahimi SA, Ourmazdi H, Selseleh M, Karjalian M, Haj-Hassani G, *et al*. *In vitro* and *in vivo* activities of *Peganum harmala* extract against *Leishmania major*. J Res Med Sci 2011;16:1032-9.
29. Khaliq T, Misra P, Gupta S, Reddy KP, Kant R, Maulik PR, *et al*. Peganine hydrochloride dihydrate an orally active antileishmanial agent. Bioorg Med Chem Lett 2009;19:2585-6.
30. Jiménez J, Riverón-Negrete L, Abdullaev F, Espinosa-Aguirre J, Rodríguez-Arnaiz R. Cytotoxicity of the beta-carboline alkaloids harmine and harmaline in human cell assays *in vitro*. Exp Toxicol Pathol 2008;60:381-9.
31. Mirzaie M, Nosratabadi SJ, Amin Derakhshanfar A, Sharifi I (2007). Antileishmanial activity of *Peganum harmala* extract on the in vitro growth of Leishmania major promastigotes in comparison to a trivalent antimony drug. Veterinarski Arhivir., 77(4): 365-375.
32. Mirzaie M, Nosratabadi SJ, Derakhshanfar A, Sharifi I. Antileishmanial activity of *Peganum harmala* extract on the *in vitro* growth of *Leishmania major* promastigotes in comparison to a trivalent antimony drug. Veterinarski Arhiv 2007;77:365-75.
33. Di Giorgio C, Delmas F, Ollivier E, Elias R, Balansard G, Timon-David P. *In vitro* activity of the beta-carboline alkaloids harmane, harmine, and harmaline toward parasites of the species *Leishmania infantum*. Exp Parasitol 2004;106: 67-74.
34. Sobhani AM, Ebrahimi SA, Mahmoudian M. An *in vitro* evaluation of human DNA topoisomerase I inhibition by *Peganum harmala* L. seeds extract and its beta-carboline alkaloids. J Pharm Pharm Sci 2002;5:19-23.
35. Nafisi S, Asghari MH, Nezhadi MA, Ekhtiari MS. Possible antidiabetic effect of *Peganum harmala* on streptozocine-induced mouse. World Appl Sci J 2011;14:822-4.
36. Singh AB, Chaturvedi JP, Narender T, Srivastava AK (2008). Preliminary studied on the hypoglycemic effect of *Peganum harmala* seeds ethanol extract on normal and streptozocine induced diabetic rats. Indian J. Clin. Biochem., 23(4): 391-393.

37. Waki H, Park KW, Mitro N, Pei L, Damoiseaux R, Wilpitz DC, *et al*. The small molecule harmine is an antidiabetic cell-type-specific regulator of PPAR gamma expression. Cell Metab 2007;5:357-70.
38. Shapira Z, Terkel J, Egozi Y, Nyska A, Friedman J. Abortifacient potential for the epigeal parts of *Peganum harmala*. J Ethnopharmacol 1989;27:319-25.
39. Diba K, Gerami Shoar M, Shabatkhori M, Khorshivand Z (2011). Anti fungal activity of alcoholic extract of *Peganum harmala* seeds. J. Med. Plants Res., 5(23): 5550-5554.
40. Kiani SJ, Shamsi Shahrabadi M, Ataei A, Sajjadi N (2008). *Peganum harmala* seed extract can prevent HSV-1 replication *in vitro*. Iranian J. Virol., 2(4): 11-16.
41. Kujumgiev A, Tsvetkov AI, Serkedjieva Y, Bankov AV, Christov R, Popov S (1999). Antibacterial antifungal and antiviral activity of propolis of different geographic origin. J. Ethnopharmacol., 64: 235- 240.
42. Phillipson JD, O‟Neill MJ (1987). New leads to the treatment of protozoal infections based on natural product molecules. Acta Pharm. Nord., 1: 131-144.