

REVIEW

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Improving health benefits with considering traditional and modern health benefits of *Peganum harmala*

Mohamad Hesam Shahrajabian^{1†} , Wenli Sun^{1†}  and Qi Cheng^{1,2,3*} 

Abstract

Background: Medicinal plants are potential source of natural products that play an important role in preventing different human diseases. *P. harmala* is used traditionally as emmenagogue and an abortifacient agent in the Middle East, North of Africa and West of China. It belongs to the family of Zygophyllaceae and it is a wild growing flowering plant. Its seeds are main medicinal part of the plant.

Methods: The current searching was done by the keywords in main indexing systems including PubMed/MEDLINE, Scopus, and Institute for Scientific Information Web of Science as well as the search engine of Google Scholar. The keywords were wild rue, traditional medicine, Harman, health benefits, and pharmaceutical science.

Results: The most important uses of *P. harmala* in traditional pharmaceutical sciences are in cardiovascular, gasterointestinal, nervous, endocrine, neoplasm and tumors, pain relieving, organisms, diabetes, respiratory, disinfectant, anti-pyretic, skin and hair, rheumatism, arthritis and inflammation, and ulcers. Pharmacological effects of *P. harmala* are in cardiovascular system, nervous system, antimicrobial effects, antineoplasm, nervous system, endocrine, gastrointestinal effects, osteocytes, endocrine and respiratory system. Phenolic compounds are the main reason of antioxidant capacity.

Conclusions: Due to its pharmacological activities, *P. harmala* is a high potential medicinal herb and the suggestion is to increases by doing research in efficacy and safety.

Keywords: *Peganum harmala*, Traditional medicine, Health Benefits, Pharmaceutical Benefits

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Background

Wild rue (*P. harmala*) occurrence and classification

Medicinal plants have been used for many years as remedies for both human and animal ailments [1–5]. Aromatic and medicinal plants as the key source of complementary and alternative medicine have been recently bring many hopes in alleviating of symptomatology and curing associated with so many diseases [6–9]. *P. harmala*, commonly called Esfand, Wild rue, Syrian rue, African rue, is a plant of the family Nitrariaceae [10]. This plant is native from the eastern Iranian region west to India [11]. *P. harmala* is a traditional medicinal plant which is used for many purposes, the aim of this review is to survey on some health benefits of this traditional medicinal plant. Scientific classification of harmal is shown in Table 1.

It is considered as one of the most important medicinal plant in Iranian traditional medicine, which has various benefits such as anti infection, anti inflammation, anti tumor and anti parasite. This important multipurpose medicinal plant has many phytochemical features, and contains a number of active alkaloids, particularly beta-carbolines such as harmalol, harmaline, and harmine. The plant is perennial which can grow to approximate 0.8 m tall, and the root can reach a depth of up to 6 m [12]. This perennial herbaceous plant, branched into 5–13 stems, the leaves are palmatisected into 3–5 linear lobes which are 3–6 cms long and 1.5–3.0 mm wide. Flowers arise by 1–3 on apexes of branches which bear whitish-yellow petals in color, and the fruits are globular capsule with 3 chambers, 0.9–1.3 cm in diameter and containing 35–45 angular blackish seeds. Various parts of *P. harmala* (a) Leaves and Flowers, (b) Fruit, (c) Seeds are shown in Fig. 1.

P. harmala Nutritional Composition and Chemical Constituents

The fruits and seeds are digestive, hallucinogenic, diuretic, antipyretic, antispasmodic, emetic, nauseant, narcotic and a uterine stimulant [13, 14]. The leaves used in the treatment of asthma, colic, dysmenorrhea, hiccups, neuralgia, hysteria and rheumatism [15].

Harmine was originally isolated from seeds of *P. harmala* in 1847 having a core indole structure and a pyridine ring [16]. Faskhutdinov et al. [17] isolated two alkaloids, namely dipegine and dipeginol. Four new flavonoids of acacetin 7-O-rhamnoside, 7-O-[6-O-glucosyl-2-O-(3-acetyl-rhamnosyl)glucoside and 7-O-(2-O-rhamnosyl-2-O-glucosyl)glucoside), and the glycoflavone 2-O-rhamnosyl-2-O-glucosylcytisoside were found in the aerial parts of *P. harmala* [18]. Massoud et al. [19] expressed that the principle alkaloids present are harmaline, harmine, harmalol, and peganine. Lamchouri et al. [20] also indicated that harmaline, the active principle of the seeds of *P. harmala* and its derivatives cause visual troubles, agitation, delirium, loss of coordination and it can produce paralysis at high doses. Faridi et al. [21] showed that the major components of *P. harmala* smoke were α -pinene (60.4%), limonene (6.4%) and styrene (4.2%) and those of the volatile oil were α -pinene (72.6%), trans-verbenole (3.9%) and sabinene (2.6%). Herraiz et al. [22] stated that psychopharmacological and toxicological characteristics of *P. harmala* were attributed to quinazoline and β -carboline alkaloids. They found three major quinazoline alkaloids, namely, peganine which appeared in flowers and leaves in high levels, high amounts of deoxypeganine and peganine which found in immature and green fruits, and high amounts of deoxypeganine and peganine which discovered in immature and green fruits, and also peganine and peganine glycoside accumulated in high amount in dry seeds, while roots and stems contained low amount of quinazolines. Alkaloids of Esfand can form dangerous reaction with antihistamines, antidepressants, decongestants, expectorant and some stimulants [23–25]. Phytochemical screening in the leaves of *P. harmala* showed the presence of flavonoids, alkaloids, saponins, tannins, glycosides, terpenoids and steroids and the absence of anthraquinone. Asgarpanah and Ramezanloo [26] and Fatma et al. [27] announced that the major alkaloids detected and quantified from the intensity of the fluorescence of *P. harmala* were harmine, harmaline, harmalol and harmol. Javzan et al. [28] determined alkaloids such as 1H-cyclopenta(b)quinoline, 2,3,5,6,7,8-hexahydro-9-amino-; Vasicinone (1H-Pyrrolo[2.1-b]quinazolin-9-one,3-hydroxy-2,3-dihydro) and harmine were isolated from cultivated plant of *P. harmala*. Farouk et al. [29] and Khan et al. [30] detected alkaloids, saponins, tannins, anthraquinones, flavonoids, flavones, terpenoids, phlobatannins, chalcones and cardiac glycosides in *P. harmala*. Chemical structures of harmala alkaloids are shown in Fig. 1.

Saturated fatty acids and their derivatives composition of *P. harmala* are tetradecanoic acid, 12-Methyl

Table 1 Scientific classification of harmal (*P. harmala*)

Kingdom	Plantae
Order	Sapindales
Family	Nitrariaceae
Genus	<i>Peganum</i>
Species	<i>P. hamrala</i>
Botanical name	<i>Peganum harmala</i> L.

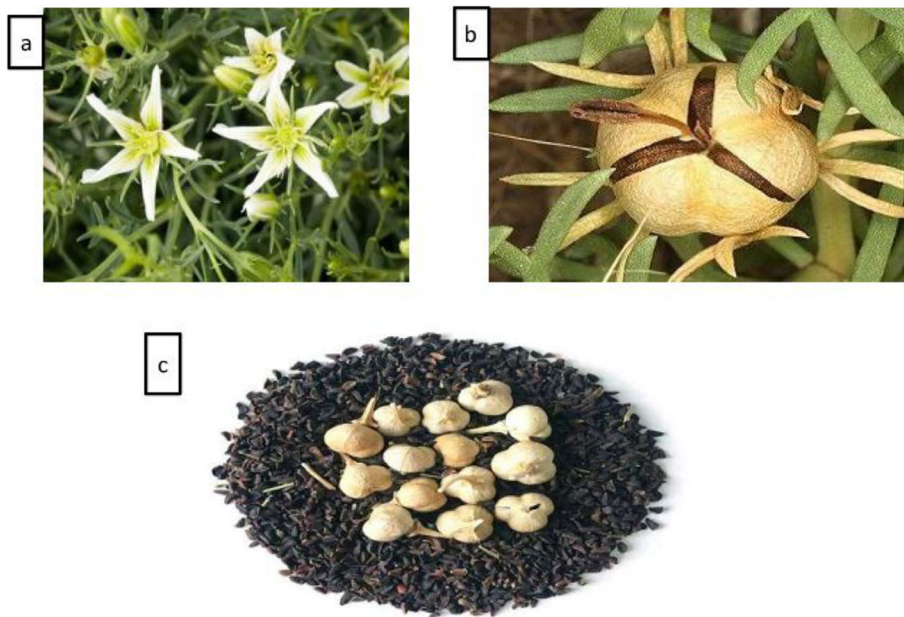


Fig. 1 Various parts of *P. harmala* **a** Leaves and Flowers, **b** Fruit, **c** Seeds

tetradecanoic acid, pentadecanoic acid, 5,9,13-Trimethyl tetradecanoic acid, tridecanoic acid, hexadecanoic acid, 2-methyl-octadecanoic acid, heptadecanoic acid and octadecanoic acid, and unsaturated fatty acids and their derivatives composition are (E)-9-dodecenoic acid, (Z)-9-Hexadecenoic acid, (Z,Z)-9,12-octadecadienoic acid and (Z,Z,Z)-9,12,15-octadecatrienoic acid [31, 32]. Non-fatty acids compounds composition of *P. harmala* detected by GC/MS are 1-octadecene, 6,10,14-trimethyl-2-pentadecanone, (E)-15-heptadecenal, xxacyclohexadecan-2-one, 1,2,2,6,8-pentamethyl-7-oxabicyclo(4.3.1)dec-8-en-10-one, hexadecane-1,2,-diol, *n*-heneicosane and eicosan-3-ol [31]. The extract of *P. harmala* has antibacterial, antifungal, antipruritic and antiprotozoal effects [33, 34]. Prashanth and John [35] concluded that the methanolic fraction of *P. harmala* found to be most effective against all tested microorganisms. Wang et al. [36] discovered that methanol extracts from the seeds of *P. harmala*, namely, (S)-vasicinone-1-O- β -d-glucopyranoside and (S)-vasicinone exhibited moderate inhibitory activity. Phytochemicals detected in the crude extracts of *P. harmala* are alkaloids, terpenoids and phenols [37–39]. Major metabolites in *P. harmala* extracts on the basis of H-NMR assignments are isoleucine, valine, threonine, alanine, lysine, acetic acid, proline, 4-hydroxyisoleucine, succinic acid, malic acid, asparagines, choline, phosphorylcholine, betaine, sucrose, β -glucose, vasicine, harmine, harmaline, vasicinone, and formic acid [40].

Medicinal Uses and Potential Health Benefits in Traditional Medicine and Modern Medicine Industry

The most important therapeutic effects of *P. harmala* are included candidiasis, anti-inflammatory, anticholinesterase, anti-bacterial, anti-microbial, anti-tumor, angiogenesis, antiparasitic, antioxidant and cytotoxicity activities, prevent of hepatoprotective, abortifacient potential, and pesticide effects [41, 42]. The most important traditional uses of *P. harmala* are cardiovascular, gastrointestinal, nervous, endocrine, neoplasm and tumors, pain relieving, diabetes, respiratory diseases, disinfectant, anti-pyretic, skin and hair, ulcers, rheumatism, arthritis and inflammation [43, 44]. Wang et al. [44] reported *P. harmala* as a traditional Chinese and Uygur medicine to treat cancer. They have found Osteoarthritis (OA) as a promising leading compound for the development of an anti-lung cancer drug. Mamedov et al. [39] found that Syrian rue used for centuries in traditional medicine and shows a potential treatment of anxiety and depression. Abolhassanzadeh et al. [45] demonstrated that topical application of Peganum oil for knee osteoarthritis is an effective pain-reducing treatment. Shatarat et al. [46] indicated that the root extract of *P. harmala* possesses antispasmodic activity and justifies its use traditionally in alleviating gastrointestinal disorders. In most parts of Iran, dried capsules mixed with other ingredients are burnt to produce scented

smoke that is used to purify the air and the mind and it is also used as a charm against the evil eye [47]. The most popular activities of *P. harmala* in traditional Iranian medicines are analgesic, intoxicating, abortive, disinfectant, anthelmintic, insect repellent, carminative and its beneficial effect in colic disorder [48]. Shahverdi et al. [49] described that *P. harmala* seeds' smoke is traditionally used in Iran as both a disinfectant agent and for all kinds of rituals against evil eye and bad luck. They have reported the antimicrobial activity of dichloromethane condensate prepared from *P. harmala* seeds (Esphand). Lamchouri et al. [50] extracted four alkaloids namely, harmalidine, harmine, peganine (vasicine) and vasicinone and discovered that *P. harmala* alkaloid inhibited the growth of four tumor cell lines, and proliferation of Jurkat cells with varying potencies, harmine was the most potent in inhibiting cell growth, and vasicinone was the most active as anti-proliferation substance. The analgesic, anti-inflammatory [51], disinfectant [52], growth promoting [53], cholesterol lowering and hepato protective effects [54] have been reported. Eini et al. [55] concluded that methanolic extract of *P. harmala* could be effectively used in rat to optimize serum lipid profile. Rahimi-Moghaddam et al. [56] showed *P. harmala* extract showed significant in vitro and in vivo antileishmanial activities. Ataee et al. [25] discovered that drinking a glass of boiled Esfand seeds may reduce blood sugar, and complaining of nausea, general weakness, abdominal pain, dizziness and several vomiting episodes. High dose of Esfand can reduce spermatogenesis in mice [57]. Aboualigalehdari et al. [58] revealed that *P. harmala* as antibiofilm herbal medicine for *C. albicans*, they have concluded that it seems to be necessary to investigate traditional herbs against pathogenic microorganisms. It has been reported that the seeds contain a red pigment used for coloring wool and carpets and also use as a spice as important aphrodisiac in traditional medicine [39]. Ismahane et al. [59] indicated that *P. harmala* essential oils have an ovicidal, adulticidal and larvicidal effects against *Ectomyelois ceratoniae* and it may be used as an alternative of chemical pesticides. Rezaei et al. [60] concluded that aqueous extract of *P. harmala* could prevent symptoms and reduced oxidative stress markers in rats with Parkinson induced by 6-hydroxydopamine. Singh et al. [61] showed that the ethanolic extract of *P. harmala* is as effective as metformin in reducing the blood glucose levels of normoglycemic and streptozotocin-induced diabetic rats. Darabpour et al. [62] noted that *P. harmala* can be assigned as a source of antibacterial compounds for treatment of infections caused by multi-drug resistant (MDR) bacterial pathogens. Chegeni et al. [63]

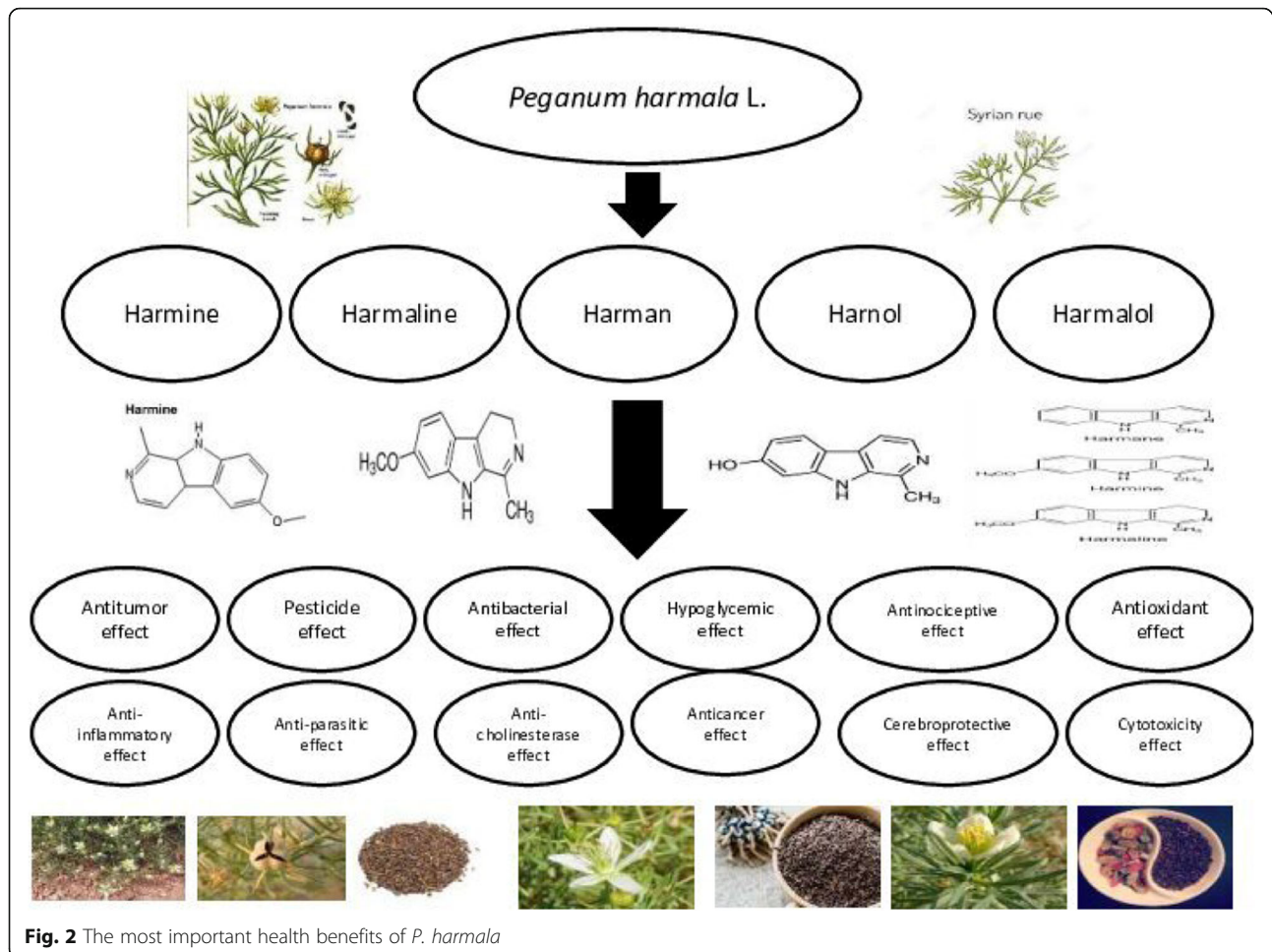
noted that ethanolic extracts of *P. harmala* could be considered a new natural compound against the *Acanthamoeba* trophozoites and cysts. Tanweer et al. [64] discovered that methanolic extract of *P. harmala* could be effectively used in broilers to optimize serum lipid profile to decrease feeding cost and to maximize gross return. Shah and Khan [65] reported that *P. harmala* seeds are antiseptic, and used is the treatment of asthma, paralysis, gastrointestinal, urinary problems, epilepsy and also menstrual disorders. Khademalhosseini et al. [66] confirmed that ethanol extract of *P. harmala* has appropriate effect on the microorganisms and the healing of skin wounds in comparison with Betadine. Mohsenipour and Hassanshahian [67] suggested that *P. harmala* extracts applied as antimicrobial agents testing bacteria particularly in biofilm forms. Shirani-Boroujeni et al. [68] noted that the application of *P. harmala* seed can be useful in reducing urinary symptoms in patients with benign prostatic hyperplasia (BPH). Berrougui et al. [69] suggested that *P. harmala* compounds could be a major source of compounds that inhibit low density lipoprotein (LDL) oxidative modification induced by copper. The seeds of *P. harmala* have been widely used for the treatment of nervous, cardiovascular, gastrointestinal, respiratory and endocrine diseases and some human ailments [70, 71]. Harmaline has multiple pharmacological impacts such as antileishmanial, antimicrobial, antiplatelet, antiplasmodial, antitumoral, hypothermic and vasorelaxant activity [72–74]. *P. harmala* alkaloids are capable of disrupting the permeability of the membranes of red blood cells of ruminants [75]. Pharmaceutical benefits of *P. harmala* are shown in Table 2. The most important health benefits of *P. harmala* are shown in Fig. 2.

Conclusions

P. harmala is a perennial herbaceous, glabrous plant mainly found in the Middle East, North Africa, and Central Asia. The plant is not usually grazed by animals due to its bitter taste. Its seeds showed that alkaloids belonging to the β -carboline family such as harmine, harmaline, harman, harmol and harmalol are responsible for a wide range of pharmacological effects. The main compounds from *P. harmala* seeds are dodecane, tetradecane, methyl dodecanoate, hexadecane, 2-octanol benzoate, heptadecane, methyl tetradecanoate, 2,6,10,14-tetramethyl pentadecane, octadecane, 2,6,10,14-tetramethyl hexadecane, nonadecane, methyl hexadecanoate, dibutyl phthalate, eicosane, methyl oleate, heneicosane, docosane, harmine and tricosane. The most important properties of *P. harmala* are anticholinesterase, anti-tumor, angiogenesis, antiparasitic effect, anti-inflammatory effect, cytotoxicity effect,

Table 2 Pharmaceutical benefits of *P. harmala*

Benefits	Mechanisms and impacts	Reference
Anti-cancer effects	<p>a. <i>P. harmala</i> alkaloids extract may be helpful in providing of new cytotoxic agents against chemo-resistant cancer cells.</p> <p>b. <i>P. harmala</i> extracts significantly decreased the growth rate and cell survival of cancer cell lines, and the extract may induce cell death regarding natural cell growth rate.</p> <p>c. <i>P. harmala</i>'s seed extract induced cell death and decreased the cell growth in the breast cancer cell line; they have suggested that herb might be useful for preventing the development of tumors.</p> <p>d. B-9-3, a semi-synthetic derivative of β-carboline, has an anti-proliferative effect against tumor cells via induction of apoptosis and inhibition of cell migration.</p>	[76–78]
Anti-viral effects	<p>a. <i>P. harmala</i> extract contains an anti-HSV-1 (herpes simplex virus type 1) substance</p> <p>b. <i>P. harmala</i> extract and its total alkaloids showed the inhibitory effect against influenza A virus replication.</p> <p>c. Its aerial parts are an effective traditional folk medicine for the treatment of cough with potent antitussive, expectorant and bronchodilating activities.</p> <p>d. Antiviral activity of the extract against influenza virus is most probably associated with inhibiting viral RNA transcription.</p> <p>e. <i>P. harmala</i> MeOH seed extract showed anti-herpes simplex virus type 2 (HSV-2) activity.</p> <p>Harmine was identified as antiviral active compound.</p>	[79–81]
Anti-inflammatory effects	<p>a. Harmine reduced inflammatory cytokines.</p> <p>b. Harmine averted inflammatory damage in the lung of LPS (lipopolysaccharides)-challenged mouse.</p> <p>c. The alkaloids, steroids, flavonoids in ethyl acetate extract of <i>P. harmala</i> seeds could be attributed for the anti-inflammatory activities.</p> <p>d. Methanol extracts of <i>P. harmala</i> has the highest anti-inflammatory activity.</p>	[24, 82, 83]
Anti-bacterial effects	<p>a. Methanol and ethanol extracts of it seems may have antibacterial activity.</p> <p>b. <i>P. harmala</i> extracts possesses strong antibacterial activity against methicillin and cefixime resistant <i>S. aureus</i> strains.</p> <p>c. Styrene and some other components with potential antimicrobial and immunomodulatory activities were formed in the smoke.</p> <p>d. Flavonoids extract of <i>P. harmala</i> may be useful to treat uropathogenic bacteria.</p> <p>e. Total alkaloidal extract of <i>P. harmala</i> seeds exhibited inhibitory impact in vitro against some phytopathogenic bacteria.</p>	[84–90]
Anti-proliferative effects	<p>a. Some triterpenoids isolated from <i>P. harmala</i> exhibited potent anti-proliferative activities.</p>	[91]
Antioxidant effects	<p>a. The methanol extract of <i>P. harmala</i> demonstrated the highest antioxidant activity and good antiviral activity against human cytomegalovirus (HCMV).</p> <p>b. The isolated protein from <i>P. harmala</i> seeds possessed strong antioxidant activity.</p>	[92, 93]
Antihyperglycemic effects	<p>a. Treatment with 4-HPA (4-hydroxypipercolic acid) stimulated both glucose uptake and glucose transporter-4 (GLUT4) translocation from intracellular to cell surface in skeletal muscle cells in a concentration-dependent manner, which might be leading to antihyperglycemic effect.</p>	[94]
Antidepressant activity	<p>a. The seed extract can correct the depression and the normal state of the treated animals.</p>	[95, 96]
Herbicidal effects	<p>a. Harmaline is a potential herbicide by its inhibition of PSII activity,</p> <p>b. Hamraline inhibits multiple sites in electron transfer chain in PSII.</p>	[97–99]
Anti-tuberculosis effects	<p>a. The ethanolic extracts of <i>P. harmala</i> has anti-tuberculosis effects comparable to isoniazid and rifampin and can be good candidates for novel and safe natural products against tuberculosis.</p>	[100, 101]
Anti-diabetes effects	<p>a. <i>P. harmala</i> seed extract has good antidiabetic activity in streptozotocin-induced diabetic rats.</p> <p>b. It has benefit procedures in controlling blood glucose and harmful results induced in pancreas and liver as a natural antidiabetic drug.</p> <p>c. The harmine in the <i>P. harmala</i> seed extract exerts its anti-apoptotic effects by decreasing caspase-3 and may alleviate damages to the kidney histology in diabetic rats compared to the control group.</p>	[102–107]
Antileishmanial activity	<p>a. Leishmaniasis is a major public health problem worldwide. <i>P. haramala</i> has natural components with anti-Leishmania activity.</p>	[108, 109]
Alzheimer	<p>a. The alkaloid may be valuable source for lead compounds discovery and drugs development for treatment of memory impairment such as Alzheimer's disease.</p>	[110, 111]
Insecticidal effects	<p>a. The ethanol extract of <i>P. harmala</i> had a good insecticidal activity on <i>P. xylostella</i>.</p> <p>b. The methanol extracts of <i>P. harmala</i> has insecticidal impacts on the larvae and adults of stored grain pest.</p>	[112–114]



antioxidant effect, cerebroprotective effect, cancer effect, hepatoprotective effect, hypoglycemic effect, antibacterial effect, pesticide effect, antitumor effect, antinociceptive effects, haemosporidian infections effect and different unknown beneficial properties. This review article suggests the important potential of *P. harmala* to be employed in both new western and eastern therapeutic drugs. This review article emphasizes on the need of widespread researches and studies for covering the supplementary information and knowledge on the importance of medicinal crops. This review also suggests more evidences for other researchers to use *P. harmala* as an ancient efficacious natural drug.

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Authors' contributions

All authors contributed equally to literature research, writing manuscript, etc. The author(s) read and approved the final manuscript.

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Consent for publication

The authors consent for the publication of this review.

Competing interests

The authors declare that they have no potential conflicts of interest.

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