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A REVIEW STUDY OF THE CHEMICAL CONSTITUENTS AND THERAPEUTIC EFFECTS OF PEGANUM HARMALA L

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ABSTRACT: *Peganum harmala L was used traditionally in different populations for many medical complains. It contained a wide range of chemical constituents.. The previous studies showed that the seeds of the plant and its constituents exerted antimicrobial, anticancer, antioxidant, antidiabetic and analgesic effects and many other pharmacological activities. Harmaline, harmine, harmalol, harman, quinazoline derivatives, vasicine, vasicinone, anthroquinons and fixed oils are reported from seeds and roots of this plant. This plant is used as a medicine in Turkey, Syria, Iran, Pakistan, India, Egypt and Spain. This article presents comprehensive analyzed information on the botanical, chemical and pharmacological aspects of P. harmala.*

KEYWORDS: Peganum Harmala, Antioxidant, Antidiabeetic, Harmaline.

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.

Conventional propagation of *P. harmala* is from seed and it has several limitations, including germination [7]. Growing from a perennial woody rootstock, *P. harmala* is a bright-green, densely foliaged, herbaceous succulent. Although, its smooth many-branched stems may have a spread of four feet or more, the plant is rarely over two feet tall and generally appears round and bushy in habit. As an ornamental plant, this white flowering plant, is ideal, because of its low maintenance and drought tolerance [7]. Its leaves are two inches long, born singly and finely divided into long narrow segments. Each year between June and August, *P. harmala* produces many single white conspicuous flowers .Measures one to one and one-half inches across, these relatively large and showy blooms have five oblong-elliptic petals as well as five narrow sepals of slightly longer length. Each flower has the potential to develop into a fruit which is a leathery, three-valve seed capsule that stands erect on its stalk. Each capsule measures about three to eight inch in diameter and contains more than fifty dark-brown, angular seeds (Figure 1) [8].

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Figure 1. *P. harmala* seeds.

Since review and systemic analysis of chemistry, pharmacology and clinical properties of *P. harmala* have not been reported, we were prompted to provide the currently available information on traditional and local knowledge, ethno biological and ethno medi-cinal issues, identification of pharmacologically important molecules and pharmacological studies on this useful plant.

The aim of this paper is to introduce *P. harmala* as a potent medicinal plant by highlighting its traditional applications as well as the recent findings for novel pharmacological and clinical applications.

Chemical Composition

The commonly known phytochemical compounds from *P. harmala* are alkaloids, flavonoids and anthraquinones [9, 10, 11]. Total alkaloid content of *P. harmala* varied between 2 and 5%. Harmaline, harmine, harmalol, harmol and tetrahydroharmine are identified and quantified as the main beta-carboline alkaloids in *P. harmala* extracts. Seeds and roots contain the highest levels of alkaloids with low levels in stems and leaves, and absent in flowers. 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 [12]. 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 [7]. Vasicine and vasicinone are quinazoline alkaloids and were first discovered in flowers and stems of *P. harmala*. A new β-carboline alkaloid, harmalidine and pegamine which is similar to the quinazoline alkaloids have been isolated from the seeds and aerial parts of *P. harmala* [10, 13]. The aerial parts of *P. harmala* contain four new flavonoids, including acacetin 7-O-rhamnoside, 7-O-6"-O-glucosyl-2 "-O-(3"'-acetylrhamnosyl) glucoside, 7-0-(2"'-0-rhamnosyl-2"-O-glucosylglucoside) and the glycoflavone 2"'-O rhamnosyl-2 "-O-glucosylcytisoside [10]. Two new anthraquinones have been isolated from the seeds of *P. harmala* and the structures are established as 3,6-dihydroxy-8-methoxy-2-methylanthraquinone (peganone1) and 8-hydroxy-7-methoxy-2-methylanthraquinone (peganone2) [11].

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Anti-inflammatory activity

Potential in vivo acute anti-inflammatory, analgesic activities, and in vitro antioxidative capacity of this plant was evaluated. Findings demonstrate that formulation cream of *P. harmala* seeds oil has an interesting anti-inflammatory activity with a slight peripheral analgesic effect due mainly to its richness on linoleic acid, γ-tocopherol, and polyphenols and to its important antioxidant capacity [14].

Antibacterial and antifungal activities

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 [15]. 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 [16]. It is concluded that *P. harmala* and its alkaloids could probably be used for the control of antibiotic resistant isolates of bacteria [17].

Antifungal activity of *P. harmala* on 6 and 3 species of *Candida* and *Aspergillus*, (respectively) was evaluated *in vitro*. Alcoholic extract of *P. harmala* seeds showed; MIC: 0.312 mg/ml on *Candida glabrata* and MIC: 1.25 mg/ml on *C. albicans* as the highest and lowest inhibitory effects, respectively. Moreover, minimum fungicidal concentration of the extract on Candida isolates was determined in a range of 0.625 to 2.5 mg/ml [18]. The highest fungicidal effect of the extract (minimum fungicidal concentration (MFC): 0.625 mg/ml) was found on *C. glabrata*, and the lowest on *C. albicans* (MFC: 2.5 mg/ml). The assay on *Aspergilli* showed different results in the level of species. The extract was effective on *Aspergillus niger* and *Aspergillus fumigatus* as growth inhibition [18]. Anti bacteria and anti fungal activity of *P. harmala* seeds extract is mainly related to harmaline [19].

Analgesic effect

The antinociceptive action was assayed in several experimental models in mice: writhing, formalin, and hot plate tests. These result showed that the alkaloid extract of Pgh contains active analgesic principles acting both centrally and peripherally. Furthermore, this antinociceptive effect has been avoided by naloxone at a dose of 1mg/kg in the first phase of formalin and hot plate tests indicating that this extract act partly through an opioid-mediated mechanism. In conclusion, the alkaloid extract of *Peganum harmala* seems to have both central and peripheral antinociceptive activities which may be mediated by opioid receptors [20].

Antioxidant Activity

Anti-oxidative capacity of *P. harmala* leaves was evaluated by determining its effect on lipid peroxidation inhibition by ammonium thiocyanate method. In this assay, oxidation of linoleic acid was effectively inhibited by the methanol extract of *P. harmal*a leaves (75.9 ± 0.3) after incubation for 5 days. The methanol extract displayed a high antioxidant activity when compared with positive control, tocopherol (80.12 ± 0.4) [21]. This strong antioxidant activity may be predominantly related to the presence of the phenolic compounds, such as flavonoids and tannins which are found in the methanolic extract. The correlation level between the

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phenolic content and antioxidant activity between the plant organs is an interesting aspect, which supports the hypothesis that the former compounds contribute directly to antioxidant activity [21].

Antidiabetic activity

Results of the recent studies clearly indicated that the ethanolic extract of *P. harmala* seed, significantly lowered ($P<0.001$) blood glucose level in normal and diabetic rats at variable dose levels (150 and 250 mg/kg).The ethanolic extract showed a significant improvement in their ability to utilize the external sucrose load. The data clearly showed that the extract is as effective as the known oral hypoglycemic agent metformin in reducing the blood glucose concentration after a sucrose challenge in normal and streptozotocin-induced diabetic rats [22].

However, it was reported that *P. harmala* extract has no insulin secretion activity, so the possible hypoglycemic activity is not related to pancreas and maybe it affects by using or/and absorption of glucose. The weird thing which has been seen in the studies is that by increasing the dose of *P. harmala* extract, it lost its hypoglycemic activity instead of intensifying it [23].

Cardiovascular Effects

P. harmala is one of the most frequently used medicinal plants to treat hypertension and cardiac disease worldwide [24, 25]. 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,[26] Vasorelaxant [27, 28] and angiogenic inhibitory effects.[29].

Antitumor activity

Some aspects of the antineoplastic properties of the plant Peganum was investigated. Results obtained indicate that alkaloids of Peganum have a high cell toxicity in vitro. The active principle at a dose of 50 mg/kg given orally to mice for 40 days was found to have significant antitumoural activity. *Peganum harmala* alkaloids thus possess significant antitumour potential, which could prove useful as a novel anticancer therapy [30]. Reports demonstrated that *P. harmala* derivative and harmalol inhibited cell division and synthesis of DNA in a leukemic cell line K562. *P. harmala* alkaloids were effective in cessation of cell growth and had cytotoxicity activity in dose and time dependent manner. However, harmaline as the most effective agent caused some degrees of monocytic differentiation [31].

β-carbolines alkaloids could intercalate into DNA [32]. This effect may cause inhibition of DNA topoisomerases and results in cytotoxicity. The extent of DNA topoisomerase I inhibition by *P. harmala* extract and its β-carboline alkaloids has been determined by DNA relaxation assay. Results show that harmine and harmaline like harmane inhibit topoisomerase I. Order of potency of topoisomerase I inhibition by tested β-carbolines is: harmine > harmane > harmaline which is the same order of potency observed in the cytotoxicity assays reported [33, 34].

In that case, the planar ring system in harmine and harmane, which is absent in harmaline , may explain their much greater topoisomerase I inhibitory effects [33].

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Cerebroprotective activity

The harmine alkaloids from the seeds of *Peganum harmala* (TAPH) and its cerebroprotective effect on cognitive deficit mice was isolated. The results showed that it reduces the metabolism of epinephrine, 5-HT and other monoamines and enhances the action of these neurotransmitters indirectly; this adrenergic system plays an important role in learning and memory. harmine alkaloids are potential enough to utilize in the management of Neurodegenerative disorders of the type Alzheimer's diseases[36].

Histo-functional effects

Effects of *Peganum harmala* on the reproductive system and fertility using adult male albino rats was examined. The aqueous extracts of *Peganum harmala* might have adverse effects on the processes of spermatogenesis due to direct or indirect effects on somniferous tubules and or the pituitary testicular axis[37].

Toxicity

In addition to all therapeutic effects of *P. harmala*, there have been several reports of human`[38] and animal[39] intoxications induced by this plant. There are also experimental studies indicating *P. harmala* toxicity [6, 40]. 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,[41] while oral administration of these extracts showed no toxicity. There have been also the same symptoms reported in different human cases[2, 6, 41] 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 [40, 42, 43]. and can cause paralysis, liver degeneration, spongiform changes in the central nervous system, euphoria, convulsions, digestive problems (nausea, vomiting), hypothermia and bradycardia. However, therapeutic doses have been reported to be safe in a rodent model.[44].

Animal toxicity of *P. harmala*

All parts of plant are thought to be toxic. Intravenous injection (IV) of harmine and harmaline (9 mg/kg) into cattle has shown toxic effects, such as accelerated breathing and pulse and clonic muscular spasms [45]. All domesticated animals are susceptible to poisoning from *P. harmala*, camels, especially young animals are the most affected in dry seasons [46]. There are reports of severe intoxication in cattle, donkeys, sheep and horses [47]. Digestive and nervous syndromes have been reported in animals that consume a sub-lethal amount of the plant. The animal initially becomes prostrate and then anorexia, hypersalivation, vomiting and diarrhea occur. Usually, the nervous syndromes are predominant: the first signs are excitability followed by muscular trembling and stiffness, an uneasy staggering gait and accelerated breathing. Standing is impossible and the animal goes into recumbency. The animal appears in a narcotic state interrupted by occasional short periods of excitement. After a few hours, dyspnea and mydriasis are noted. Frequent urination and subnormal temperature has also been reported in cattle [47]. Abortion frequently occurs. The course of the nervous syndrome is usually short and death follows within 30 to 36 h after the onset of signs of central nervous system (CNS)

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intoxication. The chronic intoxication of cattle is characterized by anorexia, restlessness, weakness of the hind limbs and knocking of the fetlock joint.

CONCLUSIONS

The objective of this paper has been to show the recent advances in the exploration of *Peganum harmala* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *Peganum harmala* has pharmacological functions including anti-tumor effect, anti-oxidant activity, antidiabetic activity, analgesic activity, anti-inflammatory effects, and cytotoxic activity among others. Also, it has been reported that this plant has antibacterial and antifungal effects. As the current information shows, it is also possible that β-carboline alkaloids might be useful in the development of new drugs to treat various diseases. However, the present results suggest a possibility that these alkaloids can be further developed as a potential disease-curing remedy. It must be kept in mind that clinicians should remain cautious until more definitive studies demonstrate the safety, quality and efficacy of *P. harmala*. For these reasons, extensive pharmacological and chemical experiments, together with human metabolism should be a focus for future studies. Last but not the least, this article emphasizes the potential of *P. harmala* to be employed in new therapeutic drugs and provide the basis for future research on the application of medicinal plants.

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