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Toxicity of Peganum harmala: Review and a Case Report

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ABSTRACT

Peganum harmala L. is a plant, which grows in semi-arid rangeland. The plant is used traditionally as an emmenagogue and an abortifacient agent in the Middle East and North Africa. All parts of plant are thought to be toxic and sever intoxication occurs in domestic animals. Digestive and nervous syndromes have been observed in animals that consume sub-lethal amount of the plant. The toxicated animal appears in a narcotic state interrupted by occasional short period of excitement. Abortion is frequent in animals that digest this plant in a dry year. While this plant has traditionally been used in Middle East, it shows toxic effects in human. A case of human overdose with *P. harmala* seeds is reported in this paper. Symptoms experienced by our patient found to be similar to what has been reported for domestic animals.

Keywords: *abortion, human toxicity, animal toxicity, hallucination*

Plants and plant extracts have been used since the dawn of civilization by mankind. The use of ethnobotanical preparations for various reasons, justified or not, is still continued by various cultures all around the world. Considering structural and biological diversity of terrestrial plants, they offer a unique renewable resource for the discovery of potential new drugs and modern medicine has developed a rational strategy for drug discovery which involves the study of plants and plant materials based on their ethnobotanical usage [1]. However, modern textbooks usually pay less attention to them and average medical practitioner is not aware of their usage and toxicity, especially those remedies that are used by cultures other than his own. Considering current state of tourism and immigration there is no cultural boundary in the world and any medical practitioner may visit a patient who has used a drug, which he has no knowledge of. The present article is a review of toxicity and pharmacological properties of *Peganum harmala* L., which is used traditionally as an emmenagogue and an abortifacient agent in the Middle East and North Africa.

BOTANICAL DESCRIPTION

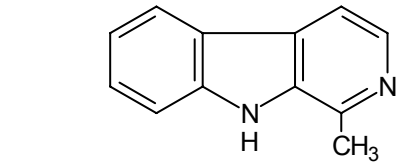
Peganum harmala L. (Zygophyllaceae) is a perennial herbaceous, glabrous plant, which may grow to 30-100 cm. Its normal habitat is semi-arid rangeland, steppe areas and sandy soils. The plant is widely distributed in the Central Asia, North Africa and Middle East and has been introduced in America and Australia. This plant is known as “Espand” in Iran, “Harmel” in North Africa and “African Rue”, “Mexican Rue” or “Turkish Rue” in United States. It has alternately spaced thong-like leaves, which have a strong deterrent odor when rumpled. Opposite to the leaves are solitary white flowers with green veins.

The flowering period is March to April. The fruits are globose capsules with 3 chambers containing many angular blackish seeds [2]. The plant is not usually grazed. Its bitter taste repels animals. However, when pasture is sparse, donkeys and other domestic animal may be attracted to and graze intermittently on this plant. All species are susceptible to poisoning from this plant, but dromedaries (camels) are the most often affected [3].

ACTIVE CONSTITUENTS

The pharmacologically active compounds of *P. harmala* are several alkaloids, which are found especially in the seeds and the roots. These include β-carbolines such as: harmine, harmaline (identical with harmidine), harmalol and harman (Fig. 1) and quinazoline derivatives: vasicine and vasicinone. The alkaloidal content of the unripe seeds is less than the ripe ones [4].

Harmaline (harmidine). $C_{13}H_{15}ON_2$ - First isolated by Göbel [5] from the seeds and roots of *P. harmala*, this is the major alkaloid of this plant. It crystallizes in colorless or pale yellow prisms and is optically inactive. This compound is slightly soluble in water, alcohol and ether, quite soluble in hot alcohol and dilute acids. Its hydrochloride dihydrate, which crystallizes as yellow needles, is moderately soluble in water and alcohol. Harmaline is almost twice as toxic as harmine and in moderate doses causes tremors and clonic convulsions but with no increase in spinal reflex excitability [6]. Lethal doses bring about convulsions, which are soon followed by motor paralysis due to the marked depressive action upon the central nervous system. Respiration is paralyzed and a decrease in body temperature occurs. The perfused heart is arrested in diastolic phase and the contractions of smooth muscle are diminished with the exception of the uterus, which may be made to contract more powerfully. Over a wide range of doses there is a reduction in blood pressure due to a pronounced weakening of the heart muscle.



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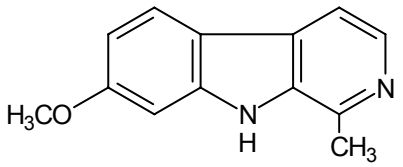

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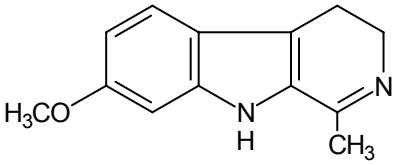

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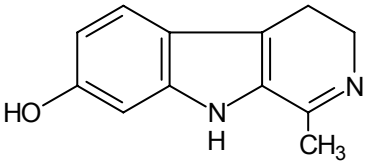

Harmalol

Fig. 1. Chemical structure of β-carboline alkaloids.

Harmine (banisterine). $C_{13}H_{12}ON_2$ - It is present in *P. harmala* and in some species of *Banisteia*, viz., *B. caapi*, *Spruce.*, *B. lutea* and *B. metallicolor*. The alkaloid is optically inactive and forms colorless rhombic prisms from methanol. It is slightly soluble in water, alcohol or ether. Solutions of its salts show a deep blue fluorescence. Pharmacologically, harmine resembles harmaline in its actions but is less toxic. The hydrochloride has been found to be highly active against Mycobacterium tuberculosis [7].

Harmalol. $C_{12}H_{12}ON_2$ - Which occurs in *P. harmala* crystallizes from water as the trihydrate. It is freely soluble in hot water, acetone or chloroform but only sparingly soluble in benzene. The alkaloid is unstable when exposed to air. Its methyl ether is harmaline [7].

Harman. $C_{12}H_{10}N_2$ - This related β-carboline alkaloid, which is first isolated from the bark of *Arariba rubra*, indigenous to Brazil; however its existence in *P. harmala* is not reported. This alkaloid is crystallized from several organic solvents as colorless prisms. It is readily soluble in methanol, alcohol, acetone, chloroform, or ether but only moderately so in hot water. It dissolves in mineral acids and exhibits a blue-violet fluorescence [7].

Vasicine (peganine). $C_{13}H_{15}ON_2$ - This quinazoline alkaloid was first isolated from the leaves of *Adhatoda vasica* Nees by Hooper and subsequently discovered in *P. harmala* under the name of Peganine. The base is optically inactive although the isolation of (-)-form from the fresh leaves of *A. vasica* and flowers and stems of *P. harmala* has been reported. The salts are readily obtained as crystals. The crude drug from *A. vasica* is used in India as a remedy for asthma and the pure alkaloid acts as a bronchodilator [8].

Vasicinone. $C_{11}H_{10}O_2N_2$ - A further alkaloid present in *Adhatoda vasica* Nees and *P. harmala*. The base forms colorless crystals from 95% alcohol. It has $[\alpha]^{22}$ -100° (c = 0.5 in $CHCl_3$) and the UV spectrum has absorption maxima at 227, 272, 302 and 315 nm. The alkaloid yields crystalline salts with mineral acids. It is an active bronchodilator [8].

ANIMAL TOXICITY

All parts of plant are thought to be toxic. Intravenous injection of harmine and harmaline (9 mg/kg) into cattle have shown toxic effects such as accelerated breathing and pulse and clonic muscular spasms [9]. The toxic doses of various alkaloids in different species are shown in the Table 1 [6]. All domesticated animals are susceptible to poisoning from *P. harmala*, camels especially young animals are the most affected in dry seasons [3]. There are reports of sever intoxication in cattle [10], donkeys [11], sheep and horses [12]. Digestive and nervous syndromes have been reported in animals that consume a sub-lethal amount of the plant [13]. The animal initially becomes prostrate and then anorexia, hyper-salivation, 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 accel-

erated 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 [10]. Abortion frequently occurs. The course of the nervous syndrome is usually short and death follows within 30-36 hours after the onset of signs of CNS intoxication. The chronic intoxication of cattle is characterized by anorexia, restlessness, weakness of the hind limbs and knocking of the fetlock joint.

In postmortem examination of animal, no distinctive lesion is observed. Rapid rigor mortis has been noted. The heart, pulmonary, renal and gastrointestinal systems are reported to be congested and sub-capsular hemorrhage in the liver has been observed [10].

Table 1. The toxic doses of various alkaloids of *P. harmala*.

Alkaloid	*Response*	*Animal*	*Dose (mg/kg)*
Harmaline	LD-sc	rats	120
Harman	LD-sc	rabbits	200
Harmine	LD_{50}-iv	mice	38
Harmine	MLD-sc	rats	200

Effects on Reproduction System and Tetratogenicity. Abortion is frequent in animals that digested this plant in a dry year [3, 14]. Shapira et al. [14] have reported the effect of methanolic extract of *P. harmala* on the reproduction of female rats. The methanolic extract at a dose of 2.5 g/kg/day, offered in food or drinking suspensions for 30 days, significantly prolonged diestrus phase by 1.0 day, while the duration of the estrous stage remained stable. The methanolic extract reduced the number of living pups and increased the number of resorption. This extract at doses, ranged 2.0 to 3.5 g/kg/day, produced a dose dependent decrease in litter size. Histopathological findings demonstrated that there was no major change in reproductive system. In all rats growing follicles and corpora lutea were observed in the ovaries. No change in the physical and nutritional status of the animals and no adverse toxicological effects were observed.

It is believed that quinazoline alkaloids (e.g. vasicine and vasicinone) are responsible for the abortifacient activity of *P. harmala* extracts [14]. It has been reported that these chemicals have a uterine stimulatory effect, apparently through the release of prostaglandins [15, 16].

HUMAN TOXICITY

While this plant has traditionally been used in Bedouin medicine as an emmenagogue and as abortifacient agent [17-19] there are few reports on its human toxic effects and syndrome. Saiah et al. [20] reported a case of overdose with *P. harmala* in a young lady (aged 27 years) who has taken 50 g of seeds of this plant for the treatment of amenorrhea. Few minutes after ingestion of seeds in a cup of coffee, signs of intoxication were observed and the patient was taken to hospital. The signs of *P. harmala* overdose comprised of hallucinations and neuro-sensorial syndromes, bradycardia and GI disturbances such as nausea and vomiting.

Para-clinical tests showed that the function of liver and kidney to be normal and the patient had a normal hematological picture. She was discharged from hospital few hours later after signs of intoxication had disappeared.

CASE REPORT

A 35 years old male patient, who was under treatment for his addiction to opium, admitted to the clinic due to gastrointestinal distress. He explained that he had consumed 1 kg of sheep testicles in the belief that it would improve his well being, but resulted in emesis and vomiting. Then to his grandmother's recommendation and according to the family tradition, he took around 150 g of seeds *P. harmala*. Due to her old age, the grandmother was not sure about the traditional dose. After that he experience gastrointestinal distress and vomited blood. On physical examination, he showed slight elevation in body temperature (37.5 °C), a pulse rate of 100 beats per minute and a low blood pressure (80/40 mmHg), convulsion, tremor (limbs and facial muscles) and visual hallucination as well as abdominal pain.

Endoscopy showed a 2.5 cm gastric ulcer at the location of anteral region in oozing state. Laboratory tests showed a mild anemia (Hb of 12.9 g/dl) due to his internal bleeding. Other biochemical parameters have found to be normal.

He was treated with infusion of 3 liters of NaCl/glucose solution and antacid (every three to four hours). After few hours, signs and symptoms of toxicity relieved and he left hospital in a stable condition. However, his treatment was continued for the peptic ulcer with omeprazol (20 mg daily) and ranitidine (150 mg bid).

CONCLUDING REMARKS

Symptoms of *P. harmala* toxicity experienced by our patient were similar to what had been reported for animals [3] and in French case [20]. These mainly consist of neuro-sensorial symptoms, hallucination, slight elevation of body temperature [21] and cardio-vascular disorder such as bradycardia and low blood pressure [22]. However, despite animal intoxication both in French [20] and our cases, signs and symptoms of intoxication relieved in few hours and patients left the hospital in good health. This difference was probably due to the amount, which has been consumed by humans compared to hungry animals. However, since this material traditionally has been used as an abortifacient agent in the Middle East [14, 15], therefore the physicians working in this region must be familiar with the signs and symptoms of its toxicity to be able to deal with the emergencies, which may arise from its illegal consumption.

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