Chapter

Intoxication by Harmel

Djafer Rachid

Abstract

Herbal medicine has taken a prominent place in the North African skincare system because of the increased installation of herbalists and healers, but unfortunately most of these do not have the required level to practice this medicine. The Harmel (*Peganum harmala* L.) belongs to the family Zygophyllaceae, which has 24 genera and 240 species. It is a herbaceous plant, perennial, glabrous, and bushy, from a height of 30–100 cm, with a thick rhizome, its strong, unpleasant odor reminiscent of that of the Rue (*Ruta graveolens*). The Harmel is a toxic plant widespread in North Africa which has an important place in traditional medicine in several indications. It is used as a sedative, antitussive, antipyretic, antirheumatic, and antihelminthic, and to treat some skin diseases. Harmel is ingested with a glass of water or mixed with honey or pounded with olive oil. The intoxications are mainly due to overdose; the absorption of a quantity of seed greater than a teaspoon causes hallucinations and vomiting. In France, Harmel as well as its compounds (Harmine, Harmaline, Harmol, and harmalol) have been classified among the astonishing substances. The clinical manifestations described in the literature include: digestive disorders, bradycardia; neurological disorders paralysis, central nervous system depression; renal disorders; and in severe cases, dyspnoea and hypothermia and hypotension.

Keywords: intoxication, Harmel, toxic plant, botanical study, toxicological analysis

1. Introduction

North Africa has one of the oldest and richest traditions associated with the use of medicinal plants where they are very important to people in many places.

In recent years, there has been a significant increase in phytotherapy, which has led to several studies on traditional herbal treatments that have identified problems of toxicity or interaction that may cause therapeutic failures or accidents.

The aim of our work is to make a complete toxicological study of Harmel, which is a plant widely used in traditional medicine in the Maghreb countries, but given its richness in toxic alkaloids of type β-carboline, it causes many accidents and intoxications in humans and animals.

2. Botanical study

2.1 Botanical description

Peganum harmala L. belongs to the Zygophyllaceae family, which has 24 genera and 240 species. It is a herbaceous plant, which is perennial, hairless, bushy, and from a height 30–100 cm tall, with thick rhizome, and it has a strong, unpleasant smell reminiscent of that of the Rue and its bitter taste repels the animals [1–3].

The erect, very rowing stems disappear in winter. They have alternate leaves, divided into narrow strips that remain green for part of the dry season.

The solitary flowers with five elliptic, solitary petals are large (25–30 mm) and yellowish-white green (**Figure 1**). They are formed by small white flowers at the axils of the branches and a globose fruit containing several flattened seeds [3, 4].

The fruits are small spherical capsules with three chambers from 6 to 10 mm in diameter that stand straight on its stem and depressed at the top. Capsules contain more than 50 small triangular seeds [5].

The seeds, dark brown in color, are small and angular and have a diameter of 3–4 mm × 2 mm (**Figure 2**) [1].

The outer seed coats are cross-linked and have a bitter taste, with a particular smell, because they contain a red pigment called "Turkey red" and a

Figure 1.
Harmel flower [4].

Figure 2.
Harmel seeds [4].

fluorescent compound. The harvest is done in summer because the seeds are rich in alkaloids [6].

2.2 Botanical classification

Branch: Spermatophytes
Sub-branch: Angiosperms
Class: Dicotyledonous
Subclass: Rosidae
Order: Sapindales
Family: Zygophyllaceae
Genre: *Peganum*
Species: *Peganum harmala* L. [3]

2.3 Appellations

Arabic name: Harmel
English name: Harmel, syrian rue, African rue, wild rue
French name: Harmel, rue syrienne, rue africaine
Spanich name: armalà, harmagà

3. Geographic distribution

Harmel is a plant that grows spontaneously throughout the world, generally in the Mediterranean area, especially in the quite dry areas in Europe (Spain, Russia, and Hungary); in North Africa in the steppe and semi-arid regions (Eastern Morocco, Northern Sahara and Algerian highlands, Tunisia, Libya steppes, and deserts of Egypt); and in Asia, it is widespread in the steppes of Iran, Pakistan, Turkestan to Tibet, and Siberia [7].

4. Chemical composition

Harmel contains the following chemical compounds:

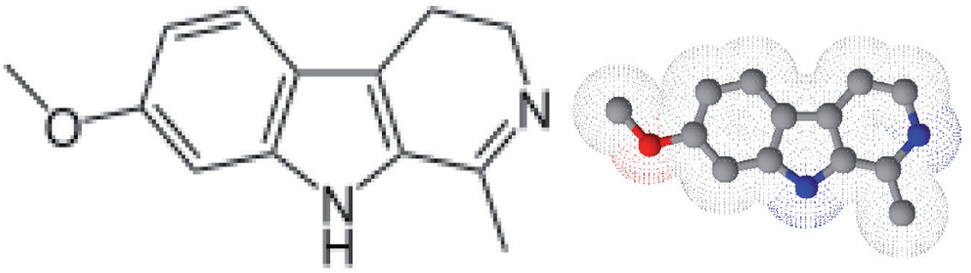
- Amino acids: phenylalanine, valine, histidine, glutamic acid
- Flavonoids: coumarin, tannins, sterols.
- Alkaloids (toxic principles): Harmane, harmine, harmaline, harmol [8, 9].

The alkaloids are more concentrated in the seeds than in the other parts of the plant (3–4%): the leaf (0.52%) and the root or the stem (0.36%).

Their content increases in summer due to the maturity of the seed [10].

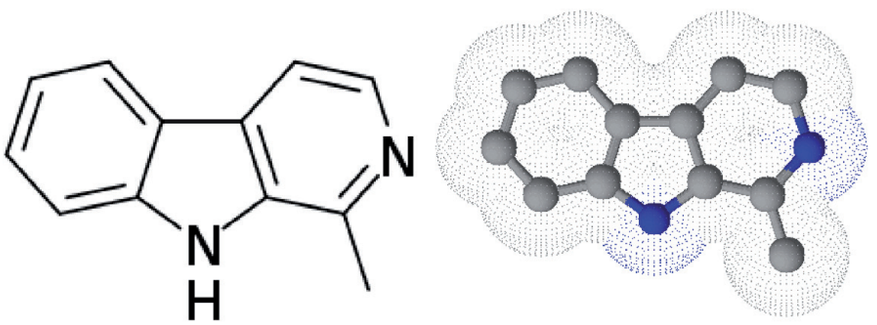
Roots contain 2% harmine and 1.4% harmol.

- Harmalin or Harmidine (3,4-dihydroharmine) or (7-methoxy-1-methyl-4,9-dihydro-3H-β-carboline) is of a general formula $C_{13}H_{14}N_2O$. It is the main alkaloid of *Peganum harmala* and the first that was isolated by Göbel from seeds and roots. This compound is slightly soluble in water and alcohol, and quite soluble in hot alcohol and dilute acids. Harmalin is almost twice more toxic than harmine. It forms the 2/3 total toxic alkaloids of the seed [8].



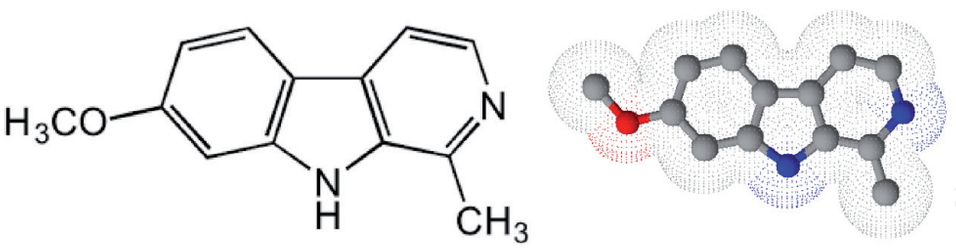
Harmalin

- Harmane (1-methyl-9-pyrido [3,4-b]indole) is of a general formula $C_{12}H_{10}N_2$. This alkaloid is crystallized in several organic solvents as colorless prisms. It is readily soluble in methanol, acetone, chloroform, or ether, but moderately soluble in hot water [8].



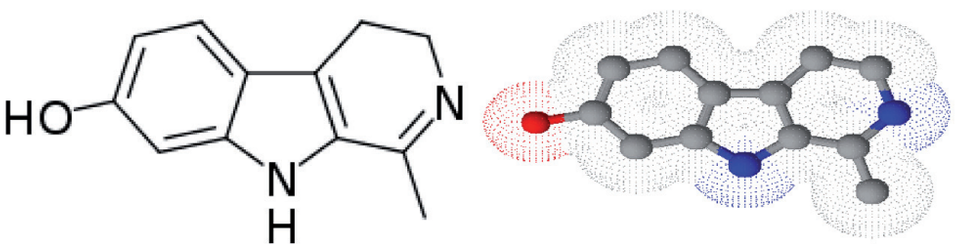
Harmane

- Harmine or Banisterin (7-methoxy-1-methyl-9-pyrido[3,4-b]indole) is of a general formula $C_{13}H_{12}N_2O$. It is slightly soluble in water, alcohol or ether.



Harmine

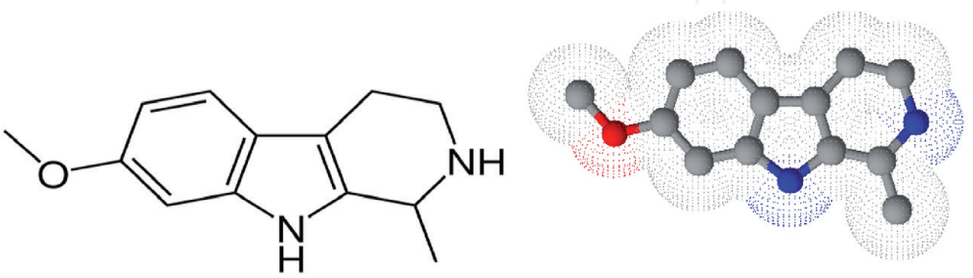
- Harmalol (1-methyl-4,9-dihydro-3H-β-carbolin-7-ol) is of a general formula $C_{12}H_{12}N_2O$. It is an unstable alkaloid when exposed to air. It is crystallized in water as tri-hydrate. It is soluble in hot water, acetone, or chloroform, but poorly soluble in benzene [8].



Harmalol

- Other β-carbolines isolated from the plant *Peganum harmala* are: Harmalicidine and tetrahydroharmine.

Harmalicidine



Tétrahydroharmine

5. Traditional use of the plant

Peganum harmala L. is considered one of the most famous medicinal plants in traditional medicine to treat several disorders.

- General disorders: hypnotic, antipyretic, analgesic, and antitussive.
- Gynecologic disorders: emmenagogue and abortifacient agent [11, 12].
- Digestive disorders: colic and hemorrhoids.
- Skin disorders: antiseptic and healing, dermatosis (eczema) and burning and blepharitis, and alopecia.
- Infectious disorders: neonatal tetanus, anthelmintic, antimalarial, and mumps.
- To treat certain nervous system disorders such as Parkinson's disease [13], in psychiatric conditions such as nervousness and insomnia in adults and children [7].
- Other diseases such as diabetes, high blood pressure, poisoning, snake venom, and rheumatism [11, 14].
- External use: the fresh plant either chopped and used in poultices, or after extraction of the juice for the composition of a liniment based on sheep fat, or use the dry plant or the seeds in the form of fumigations (to treat depression and insomnia in children) [7].

Seed oils obtained by decoction of the seeds in olive oil are very effective (rheumatic diseases). The dried plants, or the seeds, are sprayed and sieved to give the powder of the Harmel and also the decoction of roots.

- Internal use: seeds—a tea spoon, about 2.5 g, swallowed directly with a glass of water or mixed with honey or crushed with olive oil, fresh plant chopped and boiled in oil, or dry leaves in decoction.

6. Pharmacodynamics

6.1 Cardiovascular effects

In vivo studies have shown that different extracts of *Peganum harmala* where its main active alkaloids, harmine, harmalin, harman, and harmalol, have different cardiovascular effects, such as bradycardia, decreased blood pressure, peak aortic flow and contractile strength of the heart and vasodilator, and antigenic inhibitory effects [15].

6.2 Effects on the nervous system

Many in vitro and in vivo studies have indicated that alkaloids of *Peganum harmala* act on both the central and peripheral nervous system by inducing effects such as analgesia, hallucination, excitation, and antidepressant effect [16]. In addition, *Peganum harmala* β-carbolines have been shown to interact with dopamine, GABA, 5-hydroxytryptamine, benzodiazepines, and imidazoline at the level of their receptors present in the nervous system and in this way inducing their numerous psychotic pharmacological effects [17, 18].

6.3 Antibacterial, antifungal, insecticide, and antiparasitic

Different studies have shown different pharmacological effects such as antiparasitic effect, antifungal, antibacterial [18], and insecticides effects [19] of alkaloids derived from *Peganum harmala* seeds.

6.4 Effects on the immune system

Peganum harmala β-carbolines have been shown to have immunomodulatory effects in several studies [20]. Extracts of this plant have a significant anti-inflammatory effect via the inhibition of prostaglandin (mediator of inflammation).

6.5 Antidiabetic effects

Harmine is the main alkaloid of *Peganum harmala* that is involved in the antidiabetic effect. One study showed that this compound regulates the expression of the receptor Peroxysomes Gamma Proliferator-Activated (PPARγ), the main regulator of adipogenesis and the molecular target of antidiabetic drugs, by inhibition of the signaling pathway [21]. Studies have indicated that harmel extract has no activity on insulin secretion, as this hypoglycemic activity is associated with the pancreas. It affects the use and/or absorption of glucose [22].

6.6 Anticancer effects

In vitro studies have demonstrated a decrease in cell viability of cancer cells from various brain, colon, breast, lung, liver, esophagus, and stomach tissues following harmine treatment. Several researchers have shown the cytotoxicity of different *Peganum harmala* extracts in tumor cell lines in vitro and in vivo [23].

7. Toxicokinetic

7.1 Absorption

The main way of administration is the oral way by ingestion of preparation based on seeds or all parts of the plant.

After ingestion, the alkaloids are well absorbed by the gastrointestinal tract. The dermal way is used as a poultice and ointments where the seeds are mixed with olive oil which will increase the penetration of alkaloids by the skin.

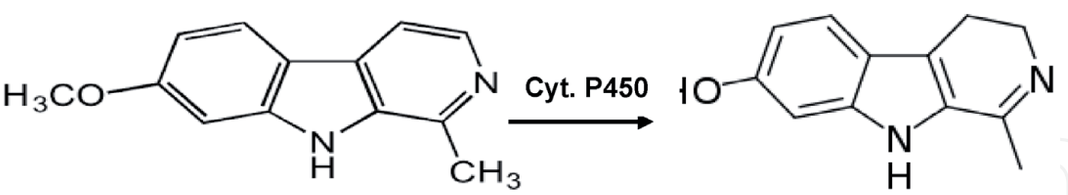
Inhalation of alkaloids by fumigation is possible because this practice is used for the therapeutic or prophylaxis of magic [14, 24].

7.2 Distribution

Alkaloids cross the blood-brain barrier to the central nervous system. They distribute throughout the body (heart, liver, kidneys, and lungs).

7.3 Metabolism

- Phase I: alkaloids undergo hepatic O-demethylation by cytochrome P450 2D6, giving harmol and harmalol.



Harmine Harmol

- Phase II: the metabolites of the oxidation phase will undergo glycuro- and sulfoconjugation processes.

- Phase III: β-carbolines alkaloids are excreted by bile and urine in conjugated form (glucuronates and sulfates); excretion of unchanged harmine should account only about 0.6% of a dose [25].

8. Mechanism of toxic action

Harmine reversibly inhibits monoamine oxidase A (MAO-A) and thus increases the central levels of amines such as noradrenaline (NA) and serotonin (5-HT) at the brain level which may explain the antidepressant effect of the plant.

Harmine is neurotoxic in vivo. Indeed, it has been shown that this injection is accompanied by tetany, convulsion movements or tremors, and these effects fade several minutes after injection [26].

All β-carbolines have in common an indole nucleus with a structural analogy to the serotonin molecule known for its important role in the functioning of the central nervous system. Harmalin and harmine are serotonin antagonists. It is likely that the hallucinogenic and behavioral modifying activity of these substances is related to this indolic structure [15].

Harmine and harmalin would exert a central anticholinergic action but at high doses can cause seizures and digestive manifestations, while harmane exerts an inhibitory action of the central dopaminergic system, inducing high-dose sedation and REM sleep disturbances [27–29].

The use of this plant for abortive purposes or to activate the term work is known. This abortive activity of harmel is due to these derivatives of quinazoline, which cause the contraction of the uterine muscle via induction of prostaglandin secretion [29].

9. Plants toxicity

9.1 In animals

Intoxication in animals is expressed by excitability, trembling, muscular rigidity, staggering gait, and jerky breathing. The animal is in an interrupted narcotic state with a short period of excitement. After a few hours, there is onset of dyspnea and mydriasis, hypothermia, and urinary disorders with abortion in case of gestation [24, 30].

- The aqueous seed extract has a myorelaxant effect on smooth rabbit and guinea pig muscles in vitro. These studies suggest that this extract has antispasmodic, antihistamine, and anti-adrenergic effects.

The laboratory animal studies have shown the following results [8]:

- Harmane: DL 50 in mice is 50 mg/kg intraperitoneally.
- Harmine: DL 50 in mice is 38 mg/kg intravenously.
- Harmalin: lethal dose in rats is 120 mg/kg subcutaneously.

9.2 In humans

Clinical observations of acute intoxications by Harmel showed that Harmalin, at a dose of 4 mg/kg, would produce psycho-mimetic effects in humans [16].

Ingestion: 10–30 min after the ingestion of a teaspoon of seeds (2.5 g) appears the following clinical signs:

- Euphoria or intoxication, violent headache, and tingling extremities.
- Hypoacusia and amaurosis neurosensory disorders and visual hallucinations (flame vision).

Then, abdominal pain is accompanied by bilious vomiting.
Four hours after ingestion the patient presents:

- Obnubilation.
- Sharp and symmetrical osteotendinous reflexes.

Seven hours after absorption, we note:

- Intense asthenia.
- Diffuse abdominal pain.
- Persistence of headaches.

These phases can change favorably in a few hours.

In severe cases, paralysis, CNS depression, dyspnea and hypothermia, and low blood pressure occur.

Inhalation: 5 min after fumigation inhalation appears intoxication and visual hallucinations.

10. Diagnosis of acute harmel intoxication

The diagnosis is based on the history and/or the appearance of nausea, vomiting, and hallucinations.

Vomiting, spontaneous or induced, and gastric washing fluids are kept in clean pots that must be kept and sent to the laboratory to identify the plant with certainty by searching for debris and alkaloids.

Send plant leaf, fruit, and seed samples used in the laboratory for plant identification.

10.1 Botanical identification

From gastric washing and/or from vomiting, recover debris (leaves, seeds, etc.). See the botanical description section and extract to search for alkaloids.

10.2 Toxicological analysis

Extract by chloroform in an alkaline medium to extract the alkaloids after drying under nitrogen, collect the residue by methanol and pass to the ultraviolet spectrophotometer [31] the maximum absorption in methanol:

- Harmane 234, 287 and 347 nm.
- Harmine 241, 301 and 336 nm.
- Harmaline 218, 260 and 376 nm.

Perform thin-layer chromatography with GF254 Silica Gel as stationary phase and elute with the mobile phase (ammonia 1.5 and methanol 100), use iodoplatinate developer reagent, and calculate alkaloid Rfs:

- Harmane 0.70.

- Harmine 0.68.
- Harmaline 0.38.

11. Treatment of acute intoxication

There is no antidotic treatment for Harmel intoxication. In the event of a coma, the symptomatic treatment must be instituted as a matter of urgency in order to maintain the vital functions [32].

11.1 Evacuator and scrubber treatment

Emergency gastric washing is used to remove parts of the plant that are not yet absorbed, and administration of activated charcoal is used to trap the rest of the plant. Induce osmotic diuresis is used in order to increase the renal elimination of alkaloids by perfusing hypertonic fluids (10% mannitol, 10% glucose serum). We need to monitor hemodynamic parameters.

11.2 Symptomatic treatment

Hospitalization in intensive care of the intoxicated provides an early respiratory resuscitation by tracheal intubation and mechanical ventilation in case of coma. Cautious warming in case of hypothermia (cover the patient and then give him a hot drink) and administration of diazepam are performed to treat seizures.

12. Conclusion

The injudicious taking of *Peganum harmala* causes clinical manifestations of intoxication; digestive disorders—bradycardia; neurological disorders—euphoria, hallucinations, generalized tremors, and even convulsive seizures; kidney disorders—uremia and anuria; and in severe cases, paralysis, central nervous system depression, dyspnea, as well as arterial hypotension.

Cases of poisoning by medicinal plants are very frequent and poorly known by the health services because the majority of victims do not come to the hospital for consultation. Today, African legislation is needed to regulate this profession of herbalists and herbalists.

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