

Case report

A case of β -carboline alkaloid intoxication following ingestion of *Peganum harmala* seed extract

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Abstract

β -Carboline alkaloids harmine, harmaline, and tetrahydroharmine can stimulate the central nervous system by inhibiting the metabolism of amine neurotransmitters, or by direct interaction with specific receptors; they are found in numerous plants, including *Peganum harmala*, *Passiflora incarnata* and *Banisteriopsis caapi*, and in the entheogen preparation Ayahuasca, which is traditionally brewed using *B. caapi* to enhance the activity of amine hallucinogenic drugs. The ingestion of plant preparations containing β -carboline alkaloids may result in toxic effects, namely visual and auditory hallucinations, locomotor ataxia, nausea, vomiting, confusion and agitation. We report a case of intoxication following intentional ingestion of *P. harmala* seed infusion; *P. harmala* seeds were bought over the Internet. The harmala alkaloids were identified by gas chromatography–mass spectrometry in the seed extract and the patient's urine. This is, to our knowledge, the first case of *P. harmala* intoxication corroborated by toxicological findings.

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1. Introduction

Peganum harmala, also known as Harmal or Syrian rue, is a perennial herbaceous, glabrous plant, that grows in semi-arid conditions, steppe areas and sandy soils, native to eastern Mediterranean region and widely distributed in Central Asia, North Africa and Middle East. It has been used as a traditional herbal remedy, mainly as an emmenagogue and an abortifacient agent [1–4]; its employ in tribal rites has been reported [5,6]. Turkey *P. harmala* is called *yüzerlik* or *üzerli*; dried capsules from this plant are hung in homes to protect against “the evil eye”. In Iran, dried capsules (known as *espaend* or *esfaend-dāneh*) – mixed with other ingredients – are burnt so as to produce a scented smoke that is used as an air as well as mind purifier and mostly as a charm against “the evil eye”. This Persian practice seems to date to pre-Islamic times [6]. Due to the psychoactive and hallucinogenic properties of its active

components (see below), the use of Harmal in ancient entheogen preparations has been postulated [7,8]. The plant has also been considered as a possible (although doubtful) candidate for the mysterious *Soma* described in the *Rig-Veda* or the *Haoma* of the old Persian Zoroastrian ceremonies [9,10].

The pharmacologically active compounds of *P. harmala* include a number of β -carboline and quinazoline alkaloids. The possible use of *P. harmala* in modern phyto-indole entheogen preparations is correlated to its content of β -carbolines: harmine, harmaline and tetrahydroharmine (THH), collectively known as harmala alkaloids. Their chemical structures are shown in Fig. 1. Harmine and harmaline are competitive and reversible inhibitors of monoamine oxidase type-A (MAO-A) enzymes, whereas THH is believed to inhibit serotonin uptake [11,12]. The harmala alkaloids are found mostly in the seeds and the roots, at a concentration of 2–7% by dry weight and are extracted as a tea formulation (infusion). In recent years, this preparation has become increasingly popular in North America and Europe and is commonly known as “Ayahuasca analog” since it contains the same harmala alkaloids of Ayahuasca [13–15].

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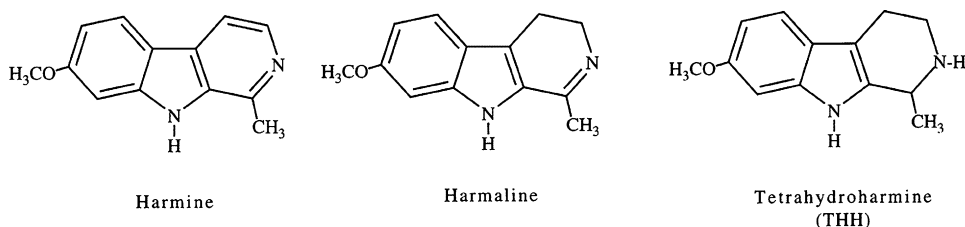


Fig. 1. Chemical structures of carboline alkaloids from *Peganum harmala*.

Ayahuasca is a psychotropic plant infusion used in shamanism as an entheogen and prepared from pounded stems of *Banisteriopsis caapi* infused together with the leaves of *Psychotria viridis* [16–18], a source of dimethyl tryptamine (DMT). Many other psychoactive plants may be added to Ayahuasca [13,17] to achieve what is called a “visionary consciousness” (projection of consciousness beyond the normal frame of reference).

DMT (a short acting psychotropic agent when administered parenterally) is not orally active possibly because of its rapid, enzymatic degradation in the gastrointestinal tract (the real mechanism of its inactivation is probably more complex) [19]. The harmala alkaloids reduce or prevent the first pass metabolism of the hallucinogenic amine(s) by inhibiting MAO-A activity [20]. The harmala alkaloids themselves are also psychoactive on their own if their dosage is sufficient [15,21,22] possibly due to direct activation of the 5-HT_{2A} or 5-HT_{2C} receptors; they also have a mild sedative effect, and interaction with benzodiazepine receptors has been postulated. However, the interactions of harmala alkaloids at the 5-HT, dopamine and benzodiazepine receptors are rather a controversial question [19,23,24].

Few intoxication cases involving harmala alkaloids have been reported in the literature. Two of them [25,26] pertain to the exclusive ingestion of *P. harmala* seeds as a traditional medication, whereas the others are due to the combined use of *P. harmala* with other substances or plant extracts [27,28]. In the only two cases of fatal, combined intoxication reported so far, the cause of death was attributed either to large nicotine dose [29] to 5-methoxy-DMT over-dosage [30]. The toxic effects of *P. harmala* in humans [25,26] have been described at the gastrointestinal (vomit, nausea), cardiac and neurological (visual hallucinations, euphoria, diffuse tremors, and convulsion) level. In animal toxicity studies [25,31], a series of effects such as paralysis, CNS depression, dyspnea, hypothermia and arterial hypotension have been observed with high dosages of *P. harmala*.

In the present report, we describe a case of a man who was poisoned with substances contained in *P. harmala* seeds bought over the Internet.

2. Case report

A 18-year-old male was admitted to a regional hospital emergency department. He asserted that he purchased “rue” seeds over the Internet and ingested a self-made infusion. The patient presented psychomotor agitation, visual hallucinations,

diffuse tremors, ataxia and vomit. A neurological exam showed that he was unable to stand upright, sleepy though responding to verbal stimulus, and presented tremor during intention and during sustained posture (upper and lower limbs). Further neurological findings were dismetria at the finger-to-nose-test and at the knee–heel test, mostly on the left side; exhaustible nystagmus on the lateral side at the examination of the cranial nerves. Blood parameters on admission were glucose 197 mg/dL, potassium 2.8 meq/L, alcohol <0.03 g/L.

Immunochemical assays for psychoactive substances (barbiturates, benzodiazepines, amphetamines, cannabinoids, cocaine, opiates, methadone, LSD by EMIT[®] and buprenorphine by ELISA) in urine yielded negative results. Subsequently, the patient’s urine and an aliquot of the seed extract, which the patient had brought with him to the emergency department, were sent to the Padova University Hospital for toxicological analysis. The patient rapidly and fully recovered and was discharged the day after.

3. Materials and methods

3.1. Chemicals

Harmine hydrochloride hydrate was purchased from Ega Chemie (Albuch, Germany) and harmaline hydrochloride dihydrate was purchased from Aldrich Chemical Company (Milwaukee, WI, USA). Stock standard solutions were prepared in methanol at a concentration of 250 µg/mL; methanolic working solutions were prepared by dilution at 25 µg/mL. A working solution of pinazepam (Zambeletti, Milan, Italy) was prepared in methanol at a concentration of 100 µg/mL and used as an internal standard (IS).

All chemicals were analytical reagent grade and all solvents were HPLC grade. Water was provided by a Milli-Q Plus (Millipore, Molsheim, France) system.

The urine and seed extract samples, originally collected at the regional hospital, were stored at 4 °C prior to analysis.

3.2. Qualitative and quantitative analysis

The first analytical approach was performed by an automatic multicolumn liquid chromatography (LC)-UV DAD system (BioRad REMEDI HS[™] Drug Profiling System, Hercules, CA, USA). The seed extract was diluted with distilled water to obtain a final concentration in the analyzable range; 1 mL of diluted sample was prepared by adding Internal Standard Combination (Biorad) and centrifuged to remove any

precipitate. The sample was run following the instrument standard procedure for urine drug screening.

In order to confirm the presence of alkaloids in the seed extract and in the urine, a more specific analytical approach was employed. We used gas chromatography/mass spectrometry (GC–MS) to samples extracted at basic pH. Five hundred microlitres fractions of the seed extract and urine samples were initially assayed, however the final quantification was based on the subsequent dilution of each sample with adequate volumes of water.

We added to the samples and/or their dilutions: water up to 1 mL volume, then 100 μ L of IS solution, KOH 0.1N to reach pH 9, and then 3.5 mL of ethyl acetate. Liquid/liquid extraction was performed for 10 min on an orbital mixer. After centrifugation at 3500 rpm for 10 min, the upper organic layer was evaporated to dryness under a nitrogen stream and the dried residue was further dissolved in 50 μ L of ethyl acetate and transferred to autosampler vials.

For the deconjugation of glucuronate and sulphate urinary metabolites, urine (diluted 1:5) was incubated with β -glucuronidase-arylsulfatase (1 mg/mL in 0.5 M sodium acetate at pH 4.0) at 65 °C for 2 h; pH was then corrected and liquid/liquid extraction was accomplished as detailed above.

For quantification, calibrators were prepared in blank urine and water at 1, 2, 5, 10 and 20 μ g/mL for harmine and harmaline; pinazepam (IS) was used as at 10 μ g/mL. Peak area ratios (analyte/IS) were calculated and subjected to least-squares linear regression.

All mass spectrometric measurements were performed on an Agilent 5973 series quadrupole mass spectrometer (Palo Alto,

CA, USA) interfaced with an Agilent 6890N series II gas chromatograph equipped with an Agilent 7673A autosampler. A Hewlett Packard HP-5MS capillary column (30 m \times 0.25 mm, 0.25 μ m film thickness) and a temperature program changing from 50 °C (2 min) to 220 °C at 15 °C/min, then to 300 °C at 30 °C/min were used, with a 1 mL/min carrier gas flow. The interface temperature was 280 °C. MS detection was performed under full scan conditions from m/z 35 to m/z 550. The injection (1 μ L) was performed in split mode (ratio 10:1), at an injector temperature of 275 °C. Quantitation was done by integration of Total Ion Current (TIC) traces.

4. Results

Harmine and harmaline were initially identified by means of LC-UV DAD in the seed infusion brought by the patient to the emergency department; the recognition of the two alkaloids was performed by comparing their elution times and absorption peaks to a library of known substances (REMEDi HS DPS Drug Library).

In order to unequivocally confirm their presence, urine and seed infusion samples were further extracted and analyzed by GC–MS in full scan mode. Identification of the analytes was based on the comparison of their full scan mass spectra with reference library mass spectra (Wiley 275 library) and, for harmine and harmaline, through a comparison with the pure standard solutions. As is shown in Figs. 2 and 3A, three sharp peaks corresponding to three β -carboline alkaloids were obtained in the chromatograms corresponding to both the

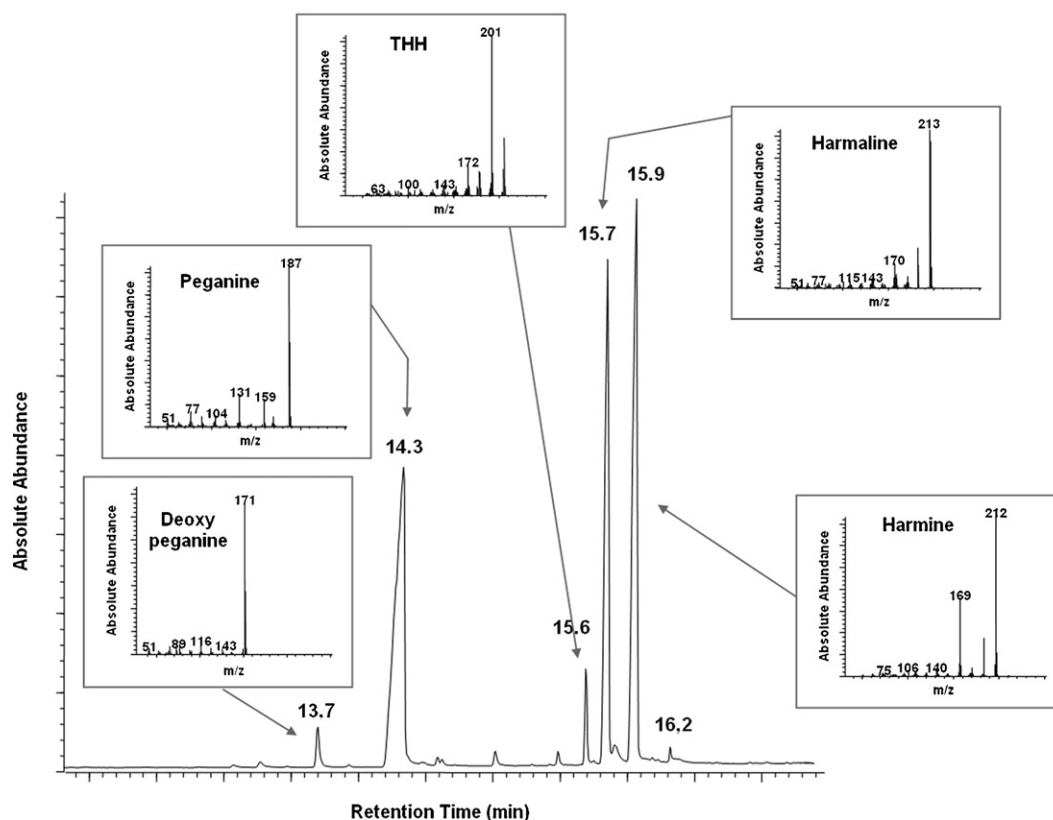


Fig. 2. GC–MS chromatogram of the patient seed extract. Peak at 16.2 min is harmol.

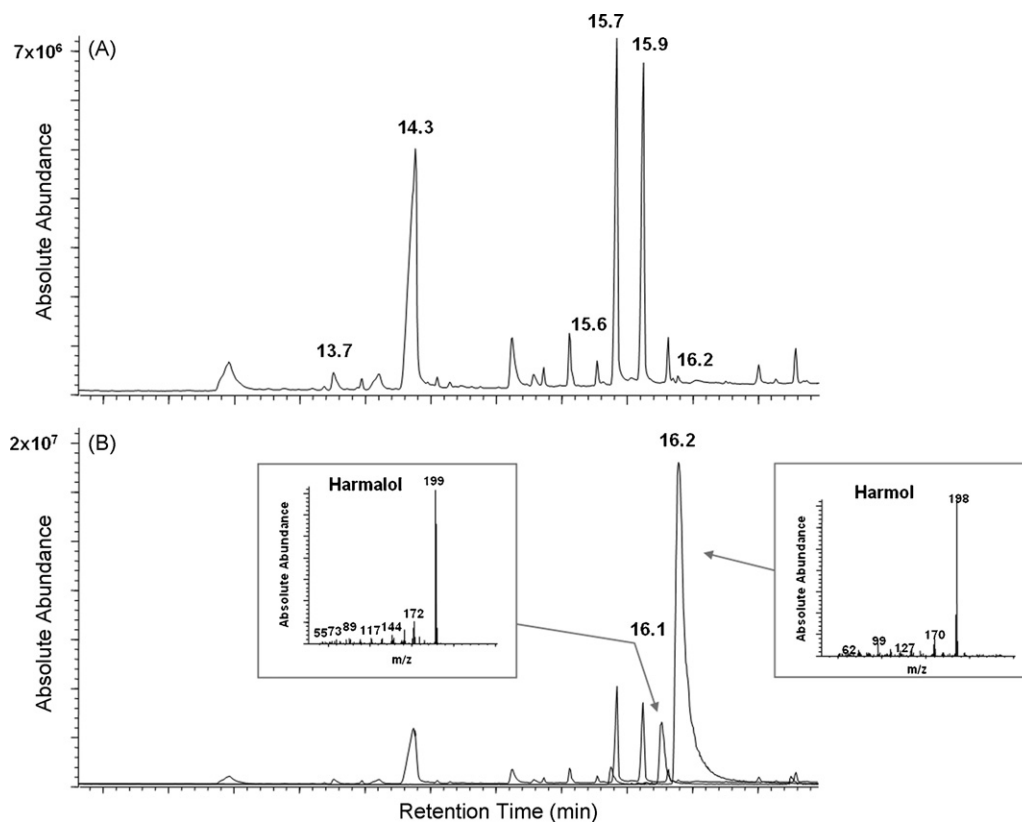


Fig. 3. GC–MS chromatogram of the patient urine before (A) and after (B) enzymatic hydrolysis to release glucuronate and sulphate metabolites.

infusion and urine samples: the retention times for THH, harmaline and harmine were respectively 15.6, 15.7 and 15.9 min. An abundant component was also detected at 14.3 min in both the infusion and the urine samples; on the basis of its mass spectrometric features and literature data [32] it could be identified as peganine, a quinazoline alkaloid of molecular weight 188 Da, while its dehydrated analogue, deoxypeganine, was detected in lower abundance at 13.7 min. Harmol (1-methyl-7-hydroxy-beta-carboline) was also identified at 16.2 min in both the seed extract and urine samples. The presence of other psychoactive drugs in both the extract and urine were excluded by immunoassays, GC–MS and high performance liquid chromatography–mass spectrometry (HPLC–MS) analysis; in particular, no trace of DMT, 5-methoxy-DMT and hallucinogen tropane alkaloids were detected.

A quantitative GC–MS method was also employed for the quantification of harmine and harmaline, exhibiting linearity in the range 1–20 $\mu\text{g}/\text{mL}$ ($r^2 = 0.9855$ for urine, 0.9998 for water). Case samples were diluted, extracted and compared to the standard curves; actual concentrations were: harmine 0.06 mg/mL and harmaline 0.45 mg/mL in urine, harmine 7.20 mg/mL and harmaline 12.00 mg/mL in the infusion.

5. Discussion

Both the infusion and the urine samples contained β -carboline alkaloids from *P. harmala*; no other hallucinogenic compound could be evidenced. We further excluded the

presence of compounds that were reportedly associated with β -carboline alkaloids in ayahuasca analog beverages: DMT, 5-methoxy-DMT, scopolamine, and atropine [13,19,28].

5.1. Infusion

According to the existing limited literature, the total alkaloid content of *P. harmala* seeds varies between 2% and 7% by dry weight [32,33] and the ratio of alkaloids in the plant may change at different stages of growth, whereas there are no data regarding the characterisation of the seed decoction. On the contrary, Ayahuasca beverages of the south western Amazon basin were extensively characterized by Rivier and Lindgren [18] that determined the presence of harmine in the range 0.07–0.19 mg/mL, THH in the range 0.015–0.09 mg/mL and harmaline in the range 0.003–0.016 mg/mL. In more recent, controlled studies for the determination of Ayahuasca pharmacokinetics, different infusions were prepared containing 0.90 mg/mL harmine, 0.06 mg/mL harmaline and 0.72 mg/mL THH [34] or 1.70 mg/mL harmine, 0.20 mg/mL harmaline and 1.07 mg/mL THH [35,36]. Harmine was also determined at a concentration of 0.179 mg/mL in an hallucinogenic tea that was allegedly prepared from an unidentified mixture of South American plants [28].

In the examined extract, the concentrations of harmine and harmaline, which were 7.20 and 12.00 mg/mL, respectively, must be considered substantially higher than those found in ayahuasca-like preparations; they lead to a ratio harmine/harmaline of 0.6 that is analogous to what is reported for the *P.*

harmala seed content (approximately 0.5) [32,33]. Regrettably, the total amount of alkaloids ingested by the patient could not be determined since full information regarding the circumstances of extract preparation (infusion, decoction?) and ingestion could not be obtained, and the THH content was not estimated due to the lack of an analytical standard.

Harmol, a component of *P. harmala* alkaloids as well as the main human metabolite of harmine [37], was also identified in the decoction. Its presence and relative abundance in *P. harmala* plants are rather controversial, with some authors defining it as a minor component [25,26] and others finding it as the major alkaloid in Turkish *P. harmala* seeds [38]. In our experiments, though lacking an absolute quantitative data, harmol seems to be present in much lower abundance compared to the other alkaloids (see Fig. 2, peak at 16.2 min). However, a home-made water preparation such as an infusion, decoction or tea, unquestionably differs in composition from the methanolic alkaloid extract prepared from seeds, and variations of alkaloid content (total and relative) correlated with plant origin, growth stages and extract preparation should be considered.

5.2. Urine

In relation to the urinary concentrations, harmine and harmaline were determined at 60 and 450 $\mu\text{g/mL}$. The literature lacks any quantitative data on β -carboline urinary concentrations. In a collective ayahuasca-like intoxication case [28], harmine was not detected in most of the urine samples and no details were given on its concentration in the few positive samples; in the combined intake described by Brush et al. [27] harmine and harmaline were reported just to be present in urine.

The urinary concentrations of unchanged alkaloids in the present case are to be considered unexpectedly high, since harmine and harmaline have been reported to be extensively metabolized by cytochrome P450 mediated *O*-demethylation to harmol and harmalol which are then excreted as glucuronates and sulphates; excretion of unchanged harmine should account only about 0.6% of a dose [37]. As expected, a GC–MS analysis after a rapid, enzymatic hydrolysis of the patient's urine allowed the detection of the two polar metabolites harmol and harmalol (see Fig. 3B) in particularly high abundance; this hydrolysis step should be envisaged whenever *P. harmala* (or ayahuasca-like) intoxication is suspected, because it will enhance the detection capabilities of metabolites in case of low β -carboline dosages.

5.3. Patient symptoms

From the toxicological point of view, the patient's symptoms can be plausibly explained by exclusive intoxication with *P. harmala* alkaloids. In the absence of data regarding the actual ingested amount, we can assume about 150–200 mL of drinkable volume (a cup of tea), that would eventually lead to the ingestion of a relatively high amount of alkaloids, respectively 1–1.3 and 1.8–2.4 g of harmine and harmaline. These amounts can be considered adequate to produce hallucinogenic effects since Pennes and Hoch [22] reported

no hallucination symptoms from harmine oral doses below 960 mg although physical symptoms began with a 400 mg dose, and harmaline was found to be hallucinogenic at oral dosages above 4 mg/kg [21]. Unfortunately, the patient's blood sample was not collected for toxicological analysis at the emergency care point, thus hindering the possibility of correlating the ingested amount, blood concentrations and toxic effects.

As above reported, harmine, harmaline, and to a lesser extent THH, inhibit MAO-A hepatic enzymes; THH inhibits serotonin deamination. β -Carbolines could modulate the levels of amine neurotransmitters in the CNS [39] and induce a series of behavioral changes; the hallucinogenic effects of harmine and harmaline are suggested to be a result of their binding to 5-HT receptors, but this is still a controversial question [19]. Originally it was proposed that the psychotropic properties of ayahuasca analogs reside in DMT, but the β -carbolines themselves may contribute to the hallucinogenic properties of the “tea” rather than simply acting as inhibitors of MAO to increase the plasma levels of DMT.

However, it must be emphasized that peganine and deoxypeganine, reportedly present in *P. harmala* seeds, were for the first time detected in an infusion-like preparation and in the patient's urine. These two quinazoline alkaloids are reported to cause a pronounced depression of cholinesterase activity in animals, with desoxypeganine showing an anticholinesterase activity being 10 times superior than peganine. In the experiments on anesthetized cats, desoxypeganine eliminated blockade of neuromuscular conductivity induced by diplicaine and conversely enhanced blockade induced by ditilin [40]. Their role in producing some of *P. harmala* intoxication symptoms should be kept in account.

The Italian legislation prohibits Ayahuasca production and consumption, but does not penalize purchase and possession of *P. harmala* seeds. Although there has been no report of fatalities as a direct consequence of harmala alkaloids intoxication, there is a concern about potentially severe intoxications because of the growing popularity in North America and Europe of Ayahuasca and analog beverages. The diffusion over the Internet of information pertaining the “know how” of illicit substances may represent a new mechanism to initiate the use of illicit substances [41,42]; this also involves our country. Drug libraries found over the Internet detail the variety of drugs, how to obtain and to use them, and how to avoid legal restrictions. The partisan sites that provide misinformation regarding the safety of these substances may lead to an increase in unsafe behavior. In some Internet sites, it is possible to buy 1 kg of Syrian rue seeds at about 50 dollars, and an “Overview of Harmala Extraction from Syrian Rue Seeds” can easily be found.

6. Conclusions

We reported a case of intoxication after the ingestion of a self-made preparation of *P. harmala* seeds bought over the Internet. The three major β -carboline alkaloids, harmine, harmaline and tetrahydroharmaline, were unequivocally iden-

tified by GC–MS in the seed extract and the patient's urine; two quinazoline alkaloids, peganine and deoxypeganine, were for the first time detected in both exhibits, whereas no trace of amine hallucinogenic compounds that are reportedly used in ayahuasca analogs (DMT or 5-methoxy-DMT) was present. The concentration of harmine and harmaline in the “tea” must be regarded as particularly high compared to data from the literature.

Harmol and harmalol, the main metabolites of harmine and harmaline, were identified in the patient's urine after enzymatic hydrolysis.

The symptoms observed in the patient can be explained by the concomitant presence of high dosage of β -carbolines, possibly interacting with specific receptors and mediating the hallucinogenesis, and two quinazoline alkaloids known to have a strong anticholinesterase activity.

This case also demonstrates that (mis)information from Internet drug libraries may affect the increase of substance abuse. Adverse outcomes related to Internet-based drug information are rarely identified and corroborated by analytical data. Therefore, clinicians must be aware of these cases in order to predict and correctly diagnose toxicity and poisoning.

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