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Review

Chemistry, pharmacology and medicinal properties of *Peganum harmala* L.

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***Peganum harmala* L. is known as Syrian rue, Wild rue and Harmal. *P. harmala* extracts are considered important for drug development, because they are reported to have numerous pharmacological activities in the Middle East, especially in Iran and Egypt. For a long time *P. harmala* has been used in traditional medicines for the relief of pain and as an antiseptic agent. *P. harmala* also have antibacterial, antifungal, antiviral, antioxidant, antidiabetic, antitumor, antileishmanial, insecticidal and cytotoxic activities and hepatoprotective and antinociceptive effects. 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*.**

Key words: *Peganum harmala*, Zygophyllaceae, phytochemical, pharmacological properties.

INTRODUCTION

Peganum harmala commonly known as Syrian rue and Wild rue is a flowering plant and is widely distributed in the Central Asia, North Africa and Middle East. It has also been introduced in America and Australia. This plant is known as “Harmal” in North Africa and “African Rue”, “Mexican Rue” or “Turkish Rue” in United States (Mahmoudian et al., 2002). It belongs to Zygophyllaceae family in the order of Zygophyllales that contains about 22 genera and more than 250 species. *Peganum* species is widely distributed in North Africa, Mediterranean, the Middle East, Pakistan, India and southern parts of Iran, and has been introduced in America and Australia (Asghari and Lockwood, 2002; Ehsanpour and Saadat, 2002; Yousefi et al., 2009). *P. harmala* has been known as “Espand” in Iran.

Conventional propagation of *P. harmala* is from seed and it has several limitations, including germination (Khawar et al., 2005). Growing from a perennial woody rootstock, *P. harmala* is a bright-green, densely foliaged, herbaceous succulent (Figure 1). 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 (Khawar et al., 2005). Its leaves are two inches long, born singly and finely divided into long narrow segments (Figure 2). Each year between June and August, *P. harmala* produces many single white conspicuous flowers (Figure 3). 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 (Figure 4). Each capsule measures about three to eight inch in diameter and contains more than fifty dark-brown, angular seeds (Figure 5) (Zargari, 1988).

People in the west Asia, burn the seeds to make smoke for keeping safe against voodoo (Rojhan, 1982). Abortion is frequent in animals that ingest this plant in dry year (Fathizad et al., 2007). The fruits are used as analgesic and antiseptic in folk medicine. For a long time, *P. harmala* has been used as a folklore medicine for treatment of various conditions, such as lumbago,

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Figure 1. *P. harmala.*



Figure 3. *P. harmala* flower and leaves.



Figure 4. *P. harmala* fruits.



Figure 5. *P. harmala* seeds.

asthma, colic, jaundice and as a stimulant emmenagogue (Bukhari et al., 2008). The seeds were known to posses hypothermic and essentially hallucinogenic properties (Sharaf et al., 1997; Lamchouri et al., 1999; Fan et al., 1997). However, its actual narcotic use in inducing visions has not yet been established beyond a doubt.

From current pharmaceutical studies, additional pharmaceutical applications of *P. harmala* have revealed anti-tumor effect (Goel et al., 2009), insecticidal effect (Goel et al., 2009), curing malaria (Goel et al., 2009), antileishmanial (Mirzaie et al., 2007), anti-spasmodic, anti-histaminic, vasorelaxant effects (Asghari and Lockwood, 2002), wound healing, anti-oxidant activity, immunomodulator properties, leukemia healing (Zaker et al., 2007), hypoglycemic effects (Singh et al., 2008), analgesic and anti-inflammatory properties, antinociceptive effects (Monsef et al., 2004), antitumor activity (Madadkar et al., 2002), hepatoprotective effect (Khaled et al., 2008) and cytotoxic activity among others. Also, it has been reported that this plant had antibacterial, antifungal and antiviral effects (Darabpour et al., 2011).

The fruits of *P. harmala* are the source of a red dye and oil (Bukhari et al., 2008). Alkaloid content of the unriped seeds is less than the ripe ones (Kartal et al., 2003). Some of the reported pharmacological effects of *P. harmala* may be attributed to its β-carboline alkaloids, mostly harmine, as well as harmaline, harmalol, harman, peganine, isopeganine, dipeganine, deoxypeganine and quinazolin derivatives such as vasicine, vasicinone and deoxyvasicinone (Mahmoudian et al., 2002; Fathizad et al., 2007). 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 medicinal issues, identification of pharmacologically important

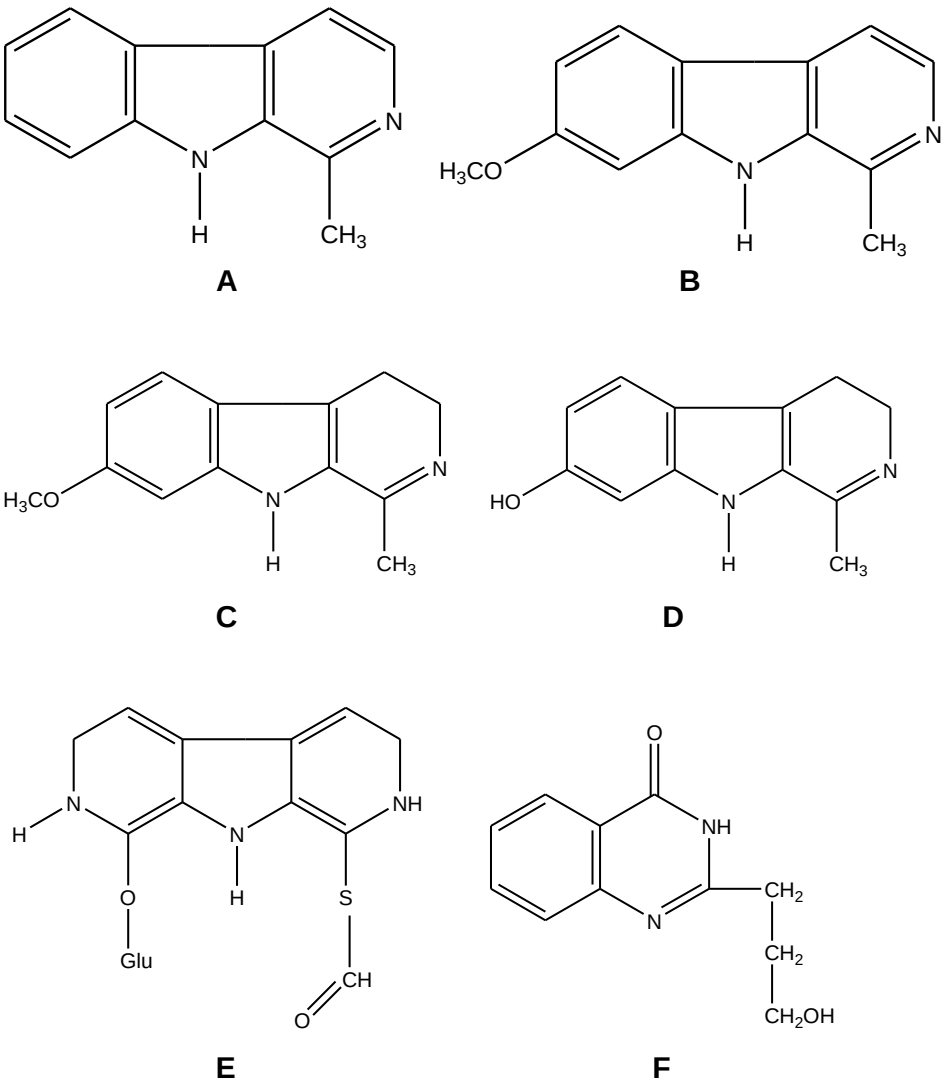


Figure 6. Structures of Harmane (A), Harmine (B), Harmaline (C), Harmalol (D), Harmalidine (E), F= Pegamine from *H. persicum* (Mahmoudian et al., 2002; Siddiqui et al., 1987; Khashimov et al., 1970).

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 (Bukhari et al., 2008; Sharaf et al., 1997; Pitre and Srivastava, 1987). Total alkaloid content of *P. harmala* varied between 2 and 5%. Harmaline, harmine, harmalol (Figure 6), 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. Harmine and harmaline accumulate in dry seeds at 4.3 and 5.6% (w/w), respectively, harmalol at 0.6% and tetrahydroharmine at 0.1% (w/w). Roots contain harmine and harmol with 2.0 and 1.4% (w/w), respectively (Herraiz et al., 2010). Peganine, isopeganine, dipeganine and deoxypeganine are also identified in the *P. harmala* (Fathizad et al., 2007; Khashimov et al., 1970).

Harmaline (harmidine) was first isolated from the seeds and roots of *P. harmala* and is the major alkaloid of this plant (Mahmoudian et al., 2002). Harmine (banisterine) is also present in *P. harmala* and pharmacologically resembles harmaline in its actions, but is less toxic.

Harmalol also occurs in this plant and its methyl ether is harmaline (Mahmoudian et al., 2002).

Vasicine and vasicinone are quinazoline alkaloids and were first discovered in flowers and stems of *P. harmala* (Mahmoudian et al., 2002). A new β-carboline alkaloid, harmalidine and pegamine (Figure 6) which is similar to the quinazoline alkaloids have been isolated from the seeds and aerial parts of *P. harmala* (Sharaf et al., 1997; Khashimov et al., 1970).

A novel β-carboline alkaloid derivative which has been isolated from the aerial parts of *P. harmala* is characterized as l-thioformyl-8- β-D-glucopyranoside-bis-2,3-dihydro-isopyridinopyrrol (Abdel-Aziz et al., 2010). 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 (Sharaf et al., 1997).

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) (Pitre and Srivastava, 1987).

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

In recent years, an explosive spread of multidrug-resistant (MDR) bacterial pathogens has become a serious concern worldwide in terms of public health and economic effects.

The antibacterial activity of different parts of *P. harmala*, including seed, root, flower, leaf and stem has been investigated and compared. Among the evaluated different parts of *P. harmala*, the seed and root extracts showed the best antibacterial activity against Gram positive bacterial species, including *Bacillus anthracis*, *Bacillus cereus*, *Bacillus pumilus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Listeria monocytogenes and Streptococcus pyogenes* and Gram negative bacterial species, including *Pseudomonas aeruginosa, Brucella melitensis*, *Proteus mirabilis*, *Salmonella typhi*, *Escherichia coli and Klebsiella pneumonia* (Darabpour et al., 2011).

The seed and root are known as reservoir parts in plants, so, it is very likely that these parts serve as arsenal of the secondary metabolites with antibacterial activity in *P. harmala*. Based on the results, the root extract has a better antibacterial activity against Gram positive bacteria except *L. monocytogenes* when compared with seed extract (Darabpour et al., 2011). It has been reported that harmane as a highly aromatic planar alkaloid exerts its antibacterial activity through intercalation with DNA (Cowan, 1999), thus, this antibacterial mechanism must be considered for active extract of *P. harmala* seed and root. The observed antibacterial activity of *P. harmala* might also be attributed to the high quantity of polyphenols, which are known to possess efficient antibacterial activity (Scherrer and Gerhar, 1971).

Results of *in vitro* antibacterial activity of different concentrations of aqueous extract of *P. harmala* seeds against *S. mutans* have shown significant activity (Minan, 2010). *P. harmala* aqueous and alcoholic extracts had the ability to inhibit the growth of *Lactobacilli* and *Candida albicans* commonly found in the mouth. The effect of 50% concentration of aqueous and alcoholic extracts had better results than 0.2% chlorohexidine for both tested microorganisms (Minan, 2010). This may be attributed to the presence of the principle alkaloids which have the ability to intercalate with DNA of the microorganisms (Phillipson and O'Neill, 1987), including harmaline, harmine, harmalol and peganine.

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 (Diba et al., 2011).

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 (Diba et al., 2011). Anti bacteria and anti fungal activity of *P. harmala* seeds extract is mainly related to harmaline (Abdel-Fattah et al., 1995).

ANTITUMOR EFFECT

Spinal-Z, the mixture of *P. harmala* seeds and leaf of *Dracocephalum kotschyii* leaves, is an Iranian ethnomedical remedy. It has been used for the treatment of various types of cancer for many years. The *in vitro* antiproliferative activities of Spinal-Z were determined using the 3-(4,5-dimethythiazol-. 2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Viability of cells treated with Spinal-Z and its components decreased in a dose dependent manner. Spinal-Z and its components showed cytotoxic effects against all cell lines tested, including A172, A2780-s, HL60, KB, K562, MCF-7, Saos-2, Hela, A2780-cp, A549, A375 and HFFF-P16. Harmine showed cytotoxicity against HL60 and K562 cell lines and this could also explain the cytotoxic effect of *P. harmala* on these cells. The leaf extract of *D. kotschyii* was able to inhibit tumor proliferation in mice (Jahanian et al., 2005).

Acute leukemia is characterized by a differentiation

arrest at an immature, still proliferating cell stage. Treatment perspectives not only include cytotoxic drugs but more interestingly using differentiation-inducing agents. Alkaloids of *P. harmala,* including harmine and harmaline are effective on the human promyelocytic cell line (HL60 cells). The result demonstrated that harmine and harmaline revealed cytostatic effect and cessation of cell growth. However, both agents at higher concentrations displayed cytotoxic effect. It was found that harmaline was the most potent compound against HL60 and in a series of tumor cell lines such as hepatocarcinoma, fibrosarcoma, myeloma, breast cancer, ovarian cancer, melanoma, etc., (Ishida et al., 1999; Al-Allaf et al., 1999; Boeira et al., 2001; Cao et al., 2005; Lamchouri et al., 2000; Jahaniani et al., 2005). In addition, some harmine derivatives showed high *in vitro* cytotoxicity and cell death via apoptosis (Chen et al., 2005). It is noted that the combination of these agents at cytostatic doses causes reduction in cell growth. In addition, harmaline showed significantly additive effect on decreasing cell proliferation when compared with ATRA (all-trans retinoic acid) alone. The main interesting point is that harmaline leads to partial differentiation into the monocytic lineage (Zaker et al., 2007).

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 (Zaker et al., 2007).

β-carbolines alkaloids could intercalate into DNA (Taira et al., 1997). 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 (Madadkar et al., 2002). 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 (Sobhani et al., 2002; Al-Allaf et al., 1999).

In that case, the planar ring system in harmine and harmane, which is absent in harmaline (Figure 6), may explain their much greater topoisomerase I inhibitory effects (Madadkar et al., 2002).

PROTECTIVE EFFECTS

Although, the cytotoxic activity of *P. harmala* has been demonstrated, the protective effects of ethanol and chloroform extracts of *P. harmala* on thiourea-induced diseases in adult male rat have also been characterized and it shows that these extracts can protect the body against the carcinogenic effects. The putative hepatoprotective effect was evaluated by the determination of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and the bilirubin level in the blood. The data showed that the extracts of *P. harmala* protected the animal against the carcinogenic effects induced by thiourea since neuron-specific enolase (NSE) and thyroglobulin (TG) levels were back to the normal range. In addition, the observed-hepatocytotoxicity after thiourea treatment was greatly reduced (AST and ALT activities were, respectively 270 and 60 IU/l and in the same order of magnitude as in the untreated rats) as well as the bilirubin levels (63 mol/l) especially for animals receiving the chloroform extract. It is suggested that extracts of *P. harmala* are efficient to reduce the toxicity induced by thiourea in male rat as far as the aforementioned parameters are concerned (Khaled et al., 2008).

ANTIDIABETIC PROPERTIES

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 (Singh et al., 2008).

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 (Hussain et al., 2004). 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 (Nafisi et al., 2011).

ANTIOXIDANT ACTIVITY

An antioxidant is defined as ‘any substance that, when present at low concentrations as compared to those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate’ (Rhee et al., 2009; Wiseman et al., 1997; Mates et al., 1999). Antioxidants are of interest to biologists and clinicians, because they help to protect the human body against damages induced by reactive free radicals generated in atherosclerosis, ischemic heart disease, cancer, Alzheimer's disease, Parkinson's disease and even in aging process (Aruoma, 2003; Hemati et al., 2010). There are many evidences that natural products and their derivatives have efficient anti-oxidative characteristics, consequently linked to anti-

cancer, hypolipidemic, anti aging and anti-inflammatory activities (Rhee et al., 2009; Wiseman et al., 1997; Hogg, 1998; Mates et al., 1999; Aruoma, 2003; Cho et al., 2006).

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) (Hayet et al., 2010).

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 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 (Hayet et al., 2010).

ANTIVIRAL ACTIVITY

Human herpes viruses are found worldwide and are among the most frequent causes of viral infections in immunoincompetent as well as in immune-compromised patients (Villarreal, 2003). Herpes simplex virus (HSV) infection is one of these infectious diseases, which occurs in far-ranging region of body. *P. harmala* seed extract had no cytotoxicity on Vero cells up to concentration of 667 µg/ml. The inhibition of virus yield showed that treating the cells with the extract 1 h after infection can significantly reduce virus titer in the first passage and inhibit completely virus production in the third passage. Regarding the HSV replication cycle, soon after infection, approximately 2 to 4 h post-infection or immediate early (IE) genes are expressed. Although, transcription of α gene requires no prior viral protein synthesis, an HSV protein brought in with the virion tegument, VP16, stimulates transcription of α gene (Knip and Howley, 2007). Therefore, inhibitory effect of the extract 1 h after infection can be caused by preventing α genes protein synthesis or possibly repressing function VP16 tegument protein. Evaluation of HSV-1 protein expression in treated infected cells by immune-fluorescence assay showed significant reduction in protein synthesis at first passage and complete repression in third passage which means that the extract can prevent viral gene expression in transcription or translation level (Kiani et al., 2008).

Different extracts of *P. harmala* leaves also had anti-cytomegalovirus (HCMV) activity in different concentrations except petroleum ether extract which did not have any antiviral activity. The most active extract was methanol extract. The active concentrations of the different extracts ranged from 25 (80% activity) to 100 mg/ml (95% activity). Methanol extract also manifested moderate antiviral activity against HCMV (Hayet et al., 2010). The antiviral activity of methanolic extract is probably due to the high phenolic content and the presence of polar substances, such as flavonoids and tannins which are known to possess antiviral activity (Abidi and Ali, 1999; Fukuchi et al., 1989; Guillen and Manzanos, 1998; Kujumgiev et al., 1999).

TOXICITY OF *P. HARMALA*

While this plant has traditionally been used in traditional medicine as an emmenagogue and as abortifacient agent (Boulus, 1983), there are few reports on its human toxic effects and syndrome. It is believed that quinazoline alkaloids (for example, vasicine and vasicinone) are responsible for the abortifacient activity of *P. harmala* extracts (Shapira et al., 1989). Few minutes after ingestion of seeds, signs of intoxication would be observed. The signs of *P. harmala* overdose comprises of hallucinations and neuro-sensorial syndromes, bradycardia and gastrointestinal (GI) disturbances, such as nausea and vomiting (Mahmoudian et al., 2002). Harmaline and harmine are toxic alkaloids characterized in the seeds of *P. harmala*. 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 (Budavari and O'Neil, 1996). 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 perfuse 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 (Mahmoudian et al., 2002).

Pharmacologically, harmine resembles harmaline in its actions, but is less toxic. The hydrochloride has been found to be highly active against Mycobacterium tuberculosis (Glasby, 1978).

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 (Puzii et al., 1980). All domesticated animals are susceptible to poisoning from *P. harmala*, camels, especially young animals are the most affected in dry seasons (El-Bahri and Chemil, 1991). There are reports of severe intoxication in cattle, donkeys, sheep and horses (Bailey, 1979). 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 (Bailey, 1979). 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) 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 (Bailey, 1979). Abortion is frequent in animals that digested this plant in a dry year (El-Bahri and Chemil, 1991).

CONCLUSION

The objective of this paper has been to show the recent advances in the exploration of *P. harmala* as phytotherapy and to illustrate its potential as a therapeutic agent. With the current information, it is evident that *P. harmala* has pharmacological functions including anti-tumor effect, anti-oxidant activity, leukemic healing, hypoglycemic effect, analgesic and anti-inflammatory properties and antinociceptive effects, antitumor and cytotoxic activity among others. Also, it has been reported that this plant has antibacterial, antifungal and antiviral 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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