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MINI REVIEW

Antitumor properties and toxicity effects of *Peganum harmala* L. (Zygophyllaceae)

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Abstract

***Peganum harmala* L. (Zygophylaceae) is a medicinal plant known to possess hypothermic and hallucinogenic properties from ancient times. Though the alkaloids identified from the species showed extensive pharmacological actions, they are highly cytotoxic. The present review summarises important findings on the antitumor properties and toxicity effects of the chemical constituents of *P. harmala*.**

Keywords: *Peganum harmala*; medicinal plant; antitumor; toxicity

Peganum harmala L. (Zygophylaceae) is a perennial shrub growing up to 1 m tall. The seeds of *P. harmala* contain about 2–6% pharmacologically active alkaloids (Hilal & Young ken, 1983), which are mostly b-carbolines such as harman, harmine, harmaline, and harmalol (El-Rifaie, 1980; Kartal, Altun, & Kurucu, 2003). Seeds and roots contained the highest levels of alkaloids with low levels in stems and leaves, and absent in flowers. Harmine and harmaline accumulated in dry seeds at 4.3% and 5.6% (w/w), respectively, harmalol at 0.6%, and tetrahydroharmine at 0.1% (w/w). Roots contained harmine and harmol with 2.0% and 1.4% (w/w), respectively (Herraiz, González, Ancín-Azpilicueta, Arán, & Guillén, 2010). In traditional medicine, *P. harmala* has been used to treat coughs, hypertension, diabetes, asthma, jaundice, lumbago, and many other human ailments (Riba *et al*., 2003; Tahraoui, El-Hilaly, Israili, & Lyoussi, 2007). Its seeds were known to possess hypothermic, and essentially hallucinogenic properties. Many studies have been conducted on the antibacterial, antifungal, antiviral and antitumour effects of *P. harmala* seeds. In Moroccan traditional medicine, seed powder is sometimes used on skin and subcutaneous tumours.

The alkaloids identified from the plants of the genus *Peganum* showed extensive pharmacological actions, such as antitumor effects (Jahaniani, Ahmed Ebrahimi, Rahbar-Roshandel, & Mahmoudian, 2005), analgesic effects (Farouk, Laroubia, Aboufatimaa, Benharref, & Chait, 2008), vasorelaxant activities (Astulla *et al*., 2008), antimicrobial activity (Prashanth & John, 1999; Arshad, Zitterl-Eglseer, Hasnain, & Hess, 2008), strong reversible inhibition of monoamine oxidase (Kim, Sablin, & Ramsay, 1997; Schwarz, Houghton, Rose, Jenner, & Lees, 2003), and inhibitive activity against acetylcholinesterase (Zheng, Youdim, & Fridkin, 2009). In the past decades, more attention has been drawn on their anticancer potencies (Boeira, da Silva, Erdtmann, & Henriques, 2001; Go¨ckler *et al*., 2009; Adhami, Farsam, & Krenn, 2011). Recently, pharmacological and therapeutic effects of *P. harmala* and its main alkaloids have been reviewed (Moloudizargari, Mikaili, Aghajanshakeri, Asghari, & Shayegh, 2013). The present attempt aims to review the antitumor properties and toxicity effects of chemical constituents of *P. harmala*.

P. harmala is a plant known since the first century A.D. and is still used for therapeutic purposes. Harmaline, the active principle of the plant seeds, and its derivatives, cause visual troubles, loss of coordination, agitation and delirium, and, at high doses, it can produce paralysis (Lamchouri *et al*., 2002). In a study designed to investigate some aspects of the antineoplastic properties of the *P. harmala,* varying concentrations of total alkaloid extracts of its seeds were tested *in vitro* on four tumoural cell-lines (Lamchouri *et al*., 1999). Results obtained indicate that alkaloids of *Peganum* have high cell toxicity *in vitro*. The

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active principle present in the plant extract at a dose of 50 mg/kg given orally to mice for 40 days was found to have significant antitumoural activity. *P. harmala* alkaloids thus possess significant antitumour potential, which could prove useful as a novel anticancer therapy. Subsequently, many studies show that the alkaloidal extract of *P. harmala* seeds is cytotoxic to several murine cell lines including UCP-Med and Med-mek carcinoma, and UCP-Med sarcoma *in vitro* and has an antitumor effect in a tumor model *in vivo* (Lamchouri *et al*., 2000; Lamchouri, 2000). Tumor proliferation was significantly reduced with *P. harmala* extracts (Lamchouri *et al*., 2000).

In another interesting study aimed at evaluating the use and manipulation of therapeutic doses of aqueous extract of *P. harmala*, Wistar rats were orally dosed acutely and the LD_{50} obtained was 2.70+/-0.05g/kg (Lamchouri *et al*., 2002). In chronic studies aqueous extract of *P. harmala* administered orally for six times a week at doses of 1, 1.35 and 2g/kg during 3 month period increased transaminases. Changes in glucose and creatinine were not significant. No significant gross changes were found at necropsy. Histologic study showed liver degeneration and spongiform changes in the central nervous system (CNS) in rats treated with 2g/kg dose but not at the therapeutic dose of 1g/kg.

The β-carboline alkaloids present in medicinal plants like *P. harmala* have recently drawn attention due to their antitumor properties. Recently, in an attempt to discover novel b-carboline alkaloids with potent antitumor activity and low neurotoxicity, nine harmine derivatives were investigated for their antitumor effects and acute toxicities in mice, and structure–activity relationship (SAR) analysis (Rihui *et al.*, 2004 ; Qi *et al*., 2004). In their study, nine harmine derivatives (including harmine) were investigated for their potential cytotoxicities against human $HepG_2$ cells using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. The harmine and its derivatives resulted in *in vitro* cytotoxicity (IC_{50}) values of 0.011–0.021 lmol/ml $HepG_2$ cells.

To recognize the structure–activity relationships, the molecular structures of the series of nine harmine derivatives (including harmine) have been studied. The tumor inhibition rates of harmine derivatives in mice bearing Lewis lung cancer, sarcoma180, or HepA tumor shows that harmine has only moderate antitumor effect, yet some of the derivatives showed inhibition rates of more than 40% while few others exhibited the highest antitumor effect among these compounds. It appears that both short alkyl and aryl substitution at R9 is favourable for antitumor activity, but aryl substitution is more favourable. The SAR analysis indicated that the formate substitution at R3 of the tricyclic skeleton reduced their neurotoxicity, while the short alkyl or aryl substitution at R9 increased the antitumor activity. All these findings indicate that compounds with both substitutions at R3 and R9 have high antitumor activity and low toxicity (Qi *et al*., 2004).

The antiproliferative activity of four alkaloids harmalacidine, harmine, peganine, and vasicinone isolated from *P. harmala* seeds and theirs computational study was investigated by Lamchouri, Toufik, Bouzzine, Hamidi, & Bouachrine (2010). These compounds were assayed *in vitro* for their effect on thymidine incorporation using Jurkat leukemia cell line at concentration of 5, 10, 25, 50, and 100 lg/ml. Their cytotoxicity was also evaluated at the concentrations indicated above on Sp2/O-Ag14 myeloma cells, Med-mek carcinoma, UCP-med Carcinoma, and UCP-med sarcoma. Results showed that vasicinone, harmine, and harmalacidine inhibited the proliferation of Jurkat, clone E6-1 cell line with significant cytotoxic effect. No noticeable effect of peganine on thymidine incorporation was observed. These *in vitro* studies have shown that harmine, b-carbolines alkaloid have more activity (Lamchouri *et al*., 2010). The harmine and β-carbolines alkaloid are highly cytotoxic and significantly inhibited tumor cell growth with apoptotic effect (Hamsa & Kuttan, 2011). This study showed that harmine significantly inhibited tumor nodule formation in the lung tissue and decreased various biochemical parameters associated with lung metastasis.

In order to identify the components in the seed extract of *P. harmala* responsible for the cytotoxic effects, four alkaloids: harmalicidine, harmine, peganine (vasicine) and vasicinone were isolated (Lamchouri *et al*., 2013). The study also focused on the cytotoxic and antiproliferative activity of the isolated alkaloids and total alkaloidal fraction (TAF) in several tumor cell lines. The alkaloids and TAF inhibited the growth of tumor cell lines to varying degrees. Of the substances evaluated, harmine was the most active compound (IC_{50} for the 4 tumor cell lines varying between 2.43 µg/ml and 18.39 µg/mL), followed by TAF (range of IC50 = 7.32 µg/mL to 13.83 µg/mL); peganine was the least active (IC_{50} = 50 µg/mL to > 100 µg/ml). In terms of antiproliferative effect, vasicinone and TAF were more potent than other substances: the concentration of vasicinone, and TAF needed to inhibit the incorporation of {3H-TDR} in the DNA cells of Jurkat, E6-1 clone by 50% (IC_{50}) were 8.60 ± 0.023 µg/mL and 8.94 ± 0.017 µg/mL, respectively, while peganine was the least active (IC_{50} >100 µg/mL). The IC_{50} values for harmalacidine (27.10 ± 0.011 µg/mL) and harmine (46.57 ± 0.011 µg/mL) were intermediate. The harmala alkaloids inhibited the growth of four tumor cell lines, and proliferation of Jurkat cells with varying potencies. Harmine was the most potent in inhibiting cell growth, and vasicinone was most active as antiproliferating substance. The TAF had significant cytotoxic as well as antiproliferating activity.

It is well known that alkaloids from *P. harmala* inhibited the growth of tumor cell lines but a study conducted in China revealed that total alkaloids from seeds of *P. harmala* possessed significant growth inhibitory effect on plants (Shao, Huang, Zhang, & Zhang, 2013). Harmaline exerted potent inhibitory effects on seedling growth of treated plants, especially dicots, inhibiting root elongation of lettuce and amaranth by 31% and 47% at a very low concentration (5 µg/mL), whereas harmine exhibited much weaker non-selective inhibitory effect on the plants. Considering the high yield and poor utilization of *P. harmala* in China, it is anticipated that this plant could be exploited as an alternative weed management tool in the future. In another study, the leaf extract and its fractions of *P. harmala* have shown pronounced mortal effect, decreased percent pupation and adult emergence of the cotton leaf worm, *Spodoptera littoralis* Boisd (Shonouda, Osman, Salama, & Ayoub, 2008). The medicinal plant *P. harmala* could be carefully applied in integrated pest management due to its strong effect on cotton leaf worm pest. Interestingly, a novel protein extracted from *P. harmala* inhibited growth of fungi such as *Alternaria alternate*, *Penicillium degitatum*, *Rhizopus stuolonifer*, and *Magnaporthe grisea*, and its antifungal activity was stable in the temperature range 4-60°C, and in the pH range 4-10 (Ma *et al*., 2013).

In a recent study (Daoud, Song, Xiao, & Shang, 2014), B-9-3, a semi-synthetic derivative of ß-carboline that is formed of two harmane molecules bound by a butyl group, exhibited anti-proliferative effect against a human lung cancer cell line, a human breast cancer cell line, and a human colorectal carcinoma cell line *via* induction of apoptosis and inhibition of cell migration. Moreover, B-9-3 inhibited tube formation in human umbilical vascular endothelial cell line (HUVEC), which indicates an anti-angiogenesis activity *in vitro*. Earlier molecular docking studies (Misra *et al*., 2008) suggest that a binding interaction with DNA topoisomerase I of *Leishmania donovani* (binding energy of -79 kcal/mol) forms a stable complex, indicating a possible role in apoptosis.

In conclusion, alkaloids from *P. harmala* show strong antitumor properties and in the mean time exhibited acute toxicity. Hence, one must be careful while using the seed extracts for traditional medicinal preparations and for any drug development programmes. In the mean time, it is to be noted that there is evidence for anti oxidative efficacy of *P. harmala* (Soliman, Abu-El-Zahab, & Alswiai, 2013; Khlifi *et al*., 2013). Analysis of purified protein from seeds of *P. harmala* plant against carbon tetrachloride (CCl_4) induced oxidative stress in rats showed strong antioxidant activity (Soliman *et al*., 2013). Further, considering the increased rate of environmental pollution, contaminants such as dioxins are very prevalent on the environment that have been linked with a variety of deleterious effects on human health including increased cancer rates. Studies proved that *P. harmala* is a candidate herbal plant for preventing dioxin mediated effects (El Gendy, Somayaji, & El-Kadi, 2010).

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