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Perspective

Recent pharmacological developments in β-carboline alkaloid "harmaline"

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ABSTRACT

Peganum harmala (L) is a perennial plant which is native of eastern Iranian and west of India but also found in different regions of western USA. A number of β-carboline compounds with therapeutic importance and different pharmacological effects, are present in this plant. Among other alkaloids, such as, harmine, harmalol and vasicine, isolated from various parts of the plant, harmaline is considered as most valuable with reference to its medicinal importance. Harmaline has been extensively studied in last decade and known to exert multiple pharmacological effects including antileishmanial, antimicrobial, antiplatelet, antiplasmodial, antitumoral, hypothermic and vasorelaxant activity. The proposed work is intended to highlight the recent pharmacological aspects of β-carboline alkaloid "harmaline".

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1. *Peganum harmala*: medicinal importance as natural source of harmaline

Harmal or Syrian rue is a trivial name of *Peganum harmala* (L) plant which is a member of the family Zygophyllaceae (Lamchouri et al., 2000). It is a perennial herbaceous plant native to dry areas ranging between the east Mediterranean to north India (Kartal et al., 2003), it is also found in the eastern Iranian region, North Africa, Middle East, China and some regions of the western USA (Farouk et al., 2008).

P. harmala is one of the few plants which are extensive and carefully used for traditional treatment of different diseases. Its seeds are used for apotropaic. The seed powder is regarded as traditional therapeutic for asthma, diarrhea, diabetes, hypertension (Airaksinen and Kari, 1981), jaundice, lumbago (Zhao et al., 2011), maceration or infusion for fever, subcutaneous tumors (Cao et al., 2007) and also for dolorous events (Asgarpanah and Ramezanloo, 2012).

P. harmala seeds contain a variety of hallucinogenic alkaloids such as harmine, harmane, harmalol, harmaline and harmalidine etc. (Fig. 1) (Cao et al., 2007). These alkaloids are also regarded as β-carboline alkaloids, due to their structural backbone. Among other carboline derivatives, harmaline (Fig. 1) acquires a prominent place, and is widely studied over the decades for its pharmacological and cytotoxic effects.

2. Pharmacological effects of harmaline

Harmaline (1-methyl-7-methoxy-4,9-dihydro β-carboline), a fluorescent psychoactive compound, was first isolated from the seeds of *P. harmala* (L) (Adachi et al., 1991) in 1841 (Goegel, 1841). Later, in 1930 it was synthesized by Hasenfratz (Spenser, 1959). Harmaline is a highly valuable alkaloid among other β-carboline alkaloids of *P. harmala* for its exciting chemistry. Although harmaline itself and its derivatives are known to cause agitation, cytotoxicity (Nakagawa et al., 2010), delirium, paralysis, loss of coordination, tremors (Shourmasti et al., 2012) and visual troubles or hallucination (Zhao et al., 2012) at an elevated dosage (Saify et al., 2004), however, its therapeutic potential and effectiveness in a wide range of pharmacological activities is also a true story. Therefore, we are reporting the following pharmacological aspects of harmaline studied by various researchers in the last decade.

2.1. Vasorelaxant

Diseases like hypertension, myocardial infarction, and atherosclerosis are the main cardiovascular diseases that are life threatening to human beings (Luo et al., 2011). *In vivo* experiments, in rat aorta pre-contracted with noradrenaline or KCl, vasorelaxation was induced in a dose dependent manner by alkaloids from

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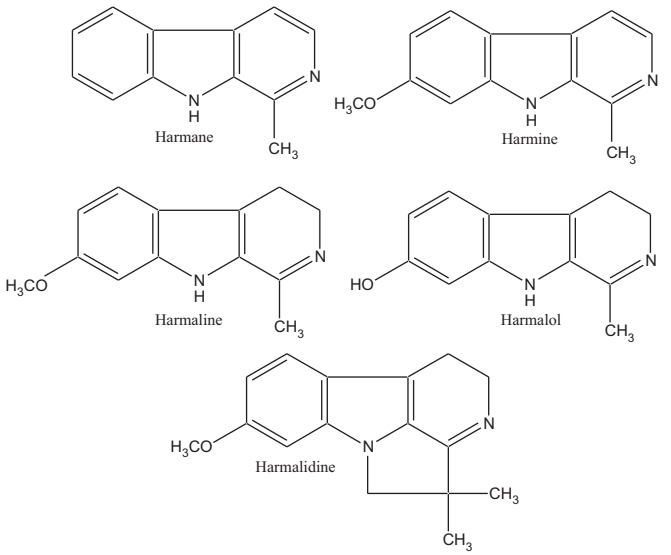

Fig. 1. Chemical structures of important β-carboline alkaloids isolated from *Peganum harmala*.

P. harmala. Vasorelaxant activities of three alkaloids were determined to be in the order of harmine > harmaline > harmalol, in isolated rat thoracic aorta preparations precontracted with phenylephrine or KCl. The vasorelaxant effect of harmine and harmaline was found to be associated with the release of nitrous oxide by the endothelial cells of rat aorta as well as these alkaloids triggered the vascular smooth muscles to inhibit the contractions induced by the activation of Ca^{2+} channels (Shi et al., 2001). Experiments on rat aorta conducted by Berrougui et al. further revealed that the vasorelaxant effect of harmaline but not harmine is related to its action on the prostacyclin pathway and on the endothelial cells to release nitrous oxide. A significant reduction in the vasorelaxant response of harmaline was reported by the removal of endothelium or pre-treatment of intact aortic ring with L-N^G-Nitroarginine methyl ester, indomethacin and Prazosin (Berrougui et al., 2006). Although the vasorelaxation effect of harmaline and its other alkaloid derivatives from *P. harmala* extract is well established in rats; however, a systematic approach is required to establish the effect in humans.

2.2. Hypothermic

Hypothermia has been found to be useful in certain clinical practices of severe brain injury, such as cardiac arrest (Jordan and Carhuapoma, 2007). Low doses of harmaline (1–10 mg/kg) injected intraperitoneally into rats caused hypothermia, while higher doses (10–30 mg/kg) induced tremor in addition to hypothermia. Intracisternal injection of harmaline into the rats decreased body temperature without inducing tremor and at much faster rate than that of intraperitoneal injection (Bruinvels, 1969). It is concluded that harmaline-induced hypothermia is at least partly localized in the central nervous system and is not associated with the tremor. Harmaline was found to be potential therapeutic for regulating the body temperature e.g. in a study on rats the seed extract from *P. harmala* was found to be effective in the regulation of the body temperature. The pretreatment with p-chlorophenylalanine (p-CPA), a 5-HT (5-hydroxytryptamine) synthesis inhibitor was observed to significantly decrease the hypothermic effect of total harmala alkaloids including harmaline. The difference in the endogenous 5-HT dependency between the *P. harmala* extract and harmaline may be explained by the following factors including the pretreatment with the dosage of p-CPA are reported to decrease endogenous 5-HT in the brain significantly and after p-CPA treatment the remaining portion of endogenous 5-HT may be sufficient for harmaline to produce hypothermia in rats. Another factor is that the 5-HT receptor is stimulated directly by harmaline. The last factor is that the harmaline induced hypothermia may involve other neurotransmitter mechanism(s), differing from the serotonergic system (Abdelfattah et al., 1995). Owing to its ability to induce hypothermic effect in rats, harmaline may be considered as a valuable replacement for the hypothermal drugs in the market today. A thorough research is however required to evaluate the suitable dosage in humans, to avoid the side effects.

2.3. Antimicrobial

β-Carboline alkaloids from *P. harmala* are known for their antimicrobial activities, against a number of pathogenic microbes e.g. *Escherichia coli, Aspergillus niger*, *Staphylococcus aureus*, *Proteus vulgaris* and *Candida albicans.* Antimicrobial activities of *P. harmala* alkaloids have been tested either individually, as binary or as a crude mixture to find whether these compounds act in a synergistic or antagonistic manner. Synergistic effects of *P. harmala* extracts, with other antimicrobial agents are well established (Schmeller and Wink, 1998). However, harmaline was found to be more effective against *P. vulgaris* and *C.albican* (Schmeller and Wink, 1998). Therefore, β-carboline alkaloids isolated from *P. harmala* can potentially act as novel antimicrobial biorationals (Arshad et al., 2008a, 2008b). Although studies are indicative of the antimicrobial tendency of harmaline, the room is still open for a vast variety of research to evaluate the antimicrobial activities of harmaline against a number of other microbes.

2.4. Antileishmanial

The visceral leishmaniasis, a disease resulting from the protozoan parasites of the genus *Leishmania*, is still considered as one of the most serious threat to humans (Wasan et al., 2009). An estimated number of over 500,000 new cases appear per annum, with a mortality rate up to 90% in untreated patients (Grimaldi et al., 1989). Evans and Croft have reported in their *in vitro* and *in vivo* studies that the harmaline is effective against antileishmanial (Evans and Croft, 1987). Harmaline is considered as the most suitable antileishmanial alkaloid as compared to its analogs such as harmane and harmine due to its non-toxicity towards the human cells. Harmaline showed weak inhibition in the growth of *Leishmania* promastigotes, however it exerted a strong antileishmanial activity toward the amastigote form of the parasite, with an IC_{50} value of 1.16 μM (Di Giorgio et al., 2004). Nontoxicity of harmaline against human cells and strong selective antileishmanial activity towards the amastogote form of the *Leishmania infantum*, suggest it as a major asset for the treatment of leishmaniasis.

2.5. Antiplasmodium

Malaria is one of the leading infectious diseases in many tropical and some temperate areas and is responsible for approximately one million deaths annually (Mang'era et al., 2012). Malaria is caused by parasites of the genus *Plasmodium*. The appearance of widespread chloroquine-resistant and multiple-drug-resistant strains of malarial parasites opens the door for the development of new therapeutic agents (Hussain et al., 2012) against malaria. Natural products are considered as potential therapeutic candidates (Sanon et al., 2003) against *Plasmodium*. A moderate *in vitro* antiplasmodial activity by harmaline against *Plasmodium Falciperum* (IC_{50}harmine 8.0 μg/mL; harmaline 25.1 μg/mL) has been reported (Astulla et al., 2008). Further research in this field

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