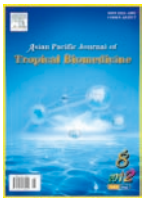
Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage:www.elsevier.com/locate/apjtb



Document heading doi:10.1016/S2221-1691(12)60116-6

A review on medicinal importance, pharmacological activity and bioanalytical aspects of beta-carboline alkaloid "Harmine"

K Patel[1], M Gadewar[2], R Tripathi[3], SK Prasad[3], Dinesh Kumar Patel[3*]

[1]*G.L.A Institute of Pharmaceutical Research, Mathura, India*
[2]*S.K.I.P.S, Warangal, A.P., India*
[3]*Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India*

ARTICLE INFO

Article history:
Received 11 January 2012
Received in revised form 16 January 2012
Accepted 23 February 2012
Available online 28 August 2012

Keywords:
Harmine
Alkaloid
Pharmacological activity
Analytical technique
Peganum harmala

ABSTRACT

Harmine, a beta-carboline alkaloid, is widely distributed in the plants, marine creatures, insects, mammalians as well as in human tissues and body fluids. Harmine was originally isolated from seeds of *Peganum harmal* in 1847 having a core indole structure and a pyridine ring. Harmine has various types of pharmacological activities such as antimicrobial, antifungal, antitumor, cytotoxic, antiplasmodial, antioxidaant, antimutagenic, antigenotoxic and hallucinogenic properties. It acts on gamma-aminobutyric acid type A and monoamine oxidase A or B receptor, enhances insulin sensitivity and also produces vasorelaxant effect. Harmine prevents bone loss by suppressing osteoclastogenesis. The current review gives an overview on pharmacological activity and analytical techniques of harmine, which may be useful for researcheres to explore the hidden potential of harmine and and will also help in developing new drugs for the treatment of various diseases.

1. Introduction

Harmine (7-methoxy-1-methyl-9H-pyrido[3, 4-b] indole) is a tricyclic beta-carboline alkaloid that was originally isolated from seeds of *Peganum harmala* in 1847. Harmine has been traditionally used for ritual and medicinal preparations in the Middle East, Central Asia and South America. Harmine is widely distributed in nature, such as in various plants, marine creatures, insects, mammalians, human tissues and body fluids. Harmine have antimicrobial, antiplasmodial, antifungal, antioxidative, antitumor, antimutagenic, cytotoxic and hallucinogenic properties[1-7]. Beta-carboline compounds act as inverse agonists at the benzodiazepine site of the gamma-aminobutyric acid type A receptors and have actions entirely opposite to those of the anxiolytic benzodiazepines. These compounds are also associated with the potentiation of monoaminergic pathways through inhibition of (MAO) A or B , blockade of reuptake sites and direct activation of monoamine receptors[8].

*Corresponding author: Dinesh Kumar Patel, Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi-221005, India.
E-mail: dkpatel.rs.phe@itbhu.ac.in

2. Overview of alkaloids

Alkaloids have been reported as one of the important groups of phytoconstituents obtained from natural sources. It plays an important role in the ecology of organisms which synthesize them. Alkaloids play an important role in the defence systems against pathogens and animals. The applications of alkaloids are not limited to biological control of herbivores but also have pharmacological, veterinary and medical importance. Alkaloids belonging to beta-carboline group possess antimicrobial, anti-HIV and antiparasitic activities[9]. In some cases, alkaloids obtained from plants may cause serious illness, injury or even death. The manner of poisoning with plants can be divided into unintentional ingestion of plant material, intentional ingestion of plant material, and ingestion of abused plant material[10].

3. Overview of beta-carboline alkaloids

Alkaloids are natural products widely distributed in plants, beverages, well-cooked foods and tobacco smoke. Beta-carboline alkaloids have been reported as normal constituents of human tissues and body fluids. They

exhibit variety of biochemical, psychopharmacological, and behavioural effects in animals and humans[9]. Beta-carboline alkaloids exhibited a wide range of psychopharmacological effects by binding to benzodiazepine, imidazoline, serotonin and opiate receptors as well as MAO inhibition[11]. Ingestion of ayahuasca (herbal preparation) containing harmine improved psychometric measures of panic and hopelessness in humans[12]. Harmine is a very important natural product due to its interesting chemistry, pharmacological importance and therapeutic potentials such as antitumor, anti-HIV and other biological activities[13]. Neurochemical and behavioral studies have shown that some beta-carboline alkaloids facilitate the dopaminergic transmission and interact with D1 and D2 dopaminergic receptors in the striatum[8]. Most beta-carboline alkaloids are known to be strong inhibitors of which metabolizes catecholamine neurotransmitters[3]. Harmine possesses antidepressant activity by interacting with MAO A and several cell-surface receptors, including serotonin receptor 2A (5-hydroxytrytamine receptor 2A, 5-HT2A)[12].

4. Pharmacological evidence of harmine

Several potential molecular targets that have been identified for the central pharmacological effects of harmine include cyclin-dependent kinases CDKs (CDK1, 2 and 5), MAO A, 5-HT2A and imidazoline receptors I1 and I2 sites. Harmine is a highly potent inhibitor of dual-specificity tyrosine-phosphorylation regulated kinase (DYRK)[1]. Harmine has been reported to have antidepressant-like actions in rodents[2]. Harmine possesses anxiolytic, behavioral effects and anti-tumor potential both *in vitro* and *in vivo*[5]. Harmine has high inhibitory affinity of DYRK1A kinase activity, suggesting that harmine could alter tau phosphorylation[6]. Harmine also has dual effects on the upstroke of the action potential of atrial muscle[14]. Additionally, harmine was reported to have cytotoxic activity against human tumor cell lines[15].

4.1. Effect of harmine against microorganisms

Pharmacological activities of harmine against *Candida albicans*, *Microsporum canis*, *Epidermophyton floccosum*, *Fusarium solani*, *Fusarium moniliforme*, *Alternaria infectoria*, *Aspergillus niger*, *Pseudallescheria boydii*, *Candida solani*, *Penicillium notatum*, *Saccharomyces cerevisiae*, *Candida lusitaniae* and *Candida tropicalis* have been investigated. Harmine did not show any remarkable inhibitory activity against all the tested organisms except *Fusarium moniliforme*[16]. Harmine was tested for its antileishmanial properties both *in vitro* and *in vivo*. Cell cycle analysis suggests that harmine does not induce apoptosis in *Leishmania donovani* promastigotes although playing a part in the cell division stage[17]. In another study, harmine was found to be effective against bacteria and protozoa[18,19]. The potential induction of a programmed cell death in *Trypanosoma b. brucei* by harmine was studied by measuring DNA fragmentation and changes in potential of mitochondrial membrane. Harmine inhibits protein biosynthesis, microtubule formation and disturbs membrane fluidity[20]. Harmine has also shown to inhibit *Trypanosoma cruzi*, the aetiological agent for Chagas disease which is one of the most serious protozoan diseases in Latin America[21].

4.2. Effect of harmine on central nervous system

Behavioural and molecular effects of harmine in rats were investigated. Chronic administration of harmine increased brain-derived neurotrophic factor protein levels in rat hippocampus[22]. Effect of harmine on animal behavior was assessed in the forced swimming and open-field tests, and the results showed harmine reduced immobility time and increased both climbing and swimming time of rats, compared to saline group. Harmine at a higher dose level also increased brain-derived neurotrophic factor protein levels in the rat hippocampus[23]. Effects of harmine on apomorphine-induced pecking behavior in chicks were also investigated. Harmine significantly decreased the pecking behavior induced by apomorphine[24]. Besides, harmine showed beneficial effects on naloxone-precipitated morphine withdrawal syndrome in morphine-dependent rats[25]. Harmine can stimulate the central nervous system by inhibiting the metabolism of amine neurotransmitters or by direct interaction with specific receptors[26]. Effects of harmine on hyperhomocysteinemia on expression of DYRK1A were investigated and the results showed that it abolished with harmine treatment[27]. Harmine has the ability to stimulate dopamine release, justifying its uses in the treatment of brain disorder[15].

4.3. Effect of harmine on enzyme systems

The effects of harmine on detoxification enzymes were studied in the polyphagous *Trichoplusia ni* and oligophagous *Papilio polyxenes*. Harmine and dietary methoxsalen increased glutathione transferase activity toward the cytosolic fraction of midgut almost two folds in *Trichoplusia ni*[28]. The effects of harmine on the food utilization efficiencies and enzymatic detoxification systems were investigated in the polyphagous noctuid *Trichoplusia ni*. Harmine reduced rates of growth and consumption[29]. Harmine is a potent inhibitor of DYRK1A, a kinase implicated in Down syndrome[30]. Harmine inhibits DYRK1A substrate phosphorylation more potently than it inhibits tyrosine autophosphorylation, providing an evidence for a role of DYRK1A in the regulation of neurite formation[31]. Harmine, an inhibitor of the forkhead box class O (FoxO) kinase DYRK1A, stimulated FoxO nuclear accumulation and DNA binding activity[32]. Harmine also stimulated ecdysone

20-monooxygenase activity as compared to the control[33].

4.4. Effect of harmine against cancer

The cytotoxicity of harmine was studied using filter paper disc technique and the results showed that complexation of metal with harmine reduced metalic toxicity[34]. Cytotoxic and genotoxic effects of harmine were investigated in V79 Chinese hamster lung fibroblasts *in vitro* using single-cell gel assay, also known as Comet assay, and the results showed that harmine increased aberrant cell frequency and induced DNA damage as evidenced by the Comet assay[35]. Effects of harmine on yeast *Saccharomyces cerevisiae* were investigated to verify putative genotoxicity, mutagenicity and recombinogenicity. Harmine is capable of inducing DNA single or double strand breaks[36]. The cytotoxicity of harmine was monitored by the brine shrimp lethality test and microdilution method was used to determine minimum inhibitory concentration and minimum bactericidal concentration of the compounds. Harmine showed cytotoxicity in the tested model[37]. The role of harmine in apoptosis of B16F-10 cells was investigated. Harmine activates both intrinsic and extrinsic pathways of apoptosis and regulates some transcription factors and pro-inflammatory cytokines[5]. The *in vivo* anti-angiogenic activity of harmine was studied using B16F-10 melanoma cells in C57BL/6 mice. Harmine decreased tumour directed capillary formation, justifying its angiogenic inhibitory potential[38]. Harmine inhibited breast cancer resistance protein (BCRP) in a BCRP overexpressing breast cancer cell line MDA-MB-231[39]. Toxicity of harmine was evaluated by cytochalasin-B blocked micronucleus assay and the viability/colony formation assay with four different human cells, including non-transformed CCD18Lu and transformed HeLa, C33A and SW480 cells. Harmine showed inhibitory effects on cell proliferation against all human carcinoma cells[11]. In cytotoxicity assays, harmine exhibited a strong inhibitory effect on the growth and proliferation of carcinoma cells whereas it had no significant effect on quiescent fibroblasts[40]. Evaluation on harmine cytotoxicity toward proliferation and differentiation of HL60 cells, alone or in combination with ATRA and G-CSF, showed that harmine reduced proliferation in a dose and time dependent manner[7]. In another study, harmine showed cytotoxicity against HL60 and K562 cell lines[41].

4.5. Effect of harmine on bone system

The investigation on effect of harmine on RAW264.7 cells showed that it inhibited multinucleated osteoclast formation induced by receptor activator of nuclear factor-kappa B ligand RANKL. Furthermore, harmine prevented RANKL-induced bone resorption in both cell and bone tissue cultures[3].

4.6. Effect of harmine against inflamation

Anti-inflammatory activity of harmine were achieved through suppression of tumor necrosis factor (TNF)-alpha and nitric oxide production in lipopolysaccharide lipopolysaccharide-stimulated mouse RAW264 and human THP-1 cells. Harmine showed stronger TNF-alpha suppressive activities than reference polyphenol and butein in RAW264 cells. Harmine was also found to suppress interleukin-6 production in RAW264 cells[42].

4.7. Pharmacokinetic study of harmine

The pharmacokinetics of the emulsion and solution containing harmine were compared in rats by cross-over test. The harmine emulsion showed a stronger tissue distributing ability than the solution. Lower radioactivity plasma concentration was found after intravenous injection of the emulsion to the rats. Therefore, it was concluded that emulsion form could reduce the toxicity and adverse effects of harmine[43].

5. Analytical techniques of harmine

For the quantification of harmine, thin layer chromatography technique was developed. Precoated silica gel G plates and toluene:ethyl acetate:methanol (6:2:2) as a solvent system were found to be suitable in the TLC analysis[44]. A high performance liquid chromatographic method for harmine was developed using a WatersTM Novapak C18 column, with a gradient solvent system of methanol-water-acetic acid[45]. Mercury (II) ions, when added to alcoholic extracts of *Peganum harmala* seeds, selectively precipitate the indole alkaloids harmine mercury complexes. This metal-mediated isolation technique of harmine was found to be relatively simple, economical and rapid[46]. Capillary liquid chromatography with MS detection for the determination of harmine was developed using C18 capillary column with a mixture of acetonitrile-ammonium formate 5 mM pH 3.6 buffer (13:87, v/v) as mobile phase[47]. A new screening method for the simultaneous determination of harmine in a human specimen was developed based on solid-phase extraction and reversed-phase liquid chromatography with photodiode array detection[48].

6. Conclusions

The use of harmine as a multi-purpose traditional medicine has been translated into several commercial applications and it is a highly valued phytoconstituent in the natural health, food and research area. Harmine has many traditional medicinal uses and pharmacological activity such as antimicrobial, anti-HIV and antiparasitic properties. Scientific studies conducted and verified many of the traditional uses including anti-inflammatory, anti-microbial, anti-parasitic and anti-cancer effects. In the

present review, an attempt has been made to compile the reported pharmacological activity, medicinal uses and analytical techniques of harmine that could be useful for the health professionals, scientists and scholars in the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of diseases in man and animals. Besides having the above mentioned pharmacological properties, it has been used as an ingredient of many herbal formulations, which are used for the treatment of various diseases. The natural phytoconstituents (Harmine) could be further studied in order to prove its benificial properties. Thus, further studies are needed to be conducted to explore the hidden potential of harmine in curing and treating various diseases. In recent years, attention has been drawn to the health promoting activity of plant foods and their active components[49-53]. Although major improvements in the quality control of harmine have been made, more attention should be paid to the optimization of the extraction and separation procedures of harmine.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Egusa H, Doi M, Saeki M, Fukuyasu S, Akashi Y, Yokota Y, et al. The small molecule harmine regulates NFATc1 and Id2 expression in osteoclast progenitor cells. *Bone* 2011; **49**(2): 264-274.

[2] Réus GZ, Stringari RB, Gonçalves CL, Scaini G, Carvalho-Silva M, Jeremias GC, et al. Administration of harmine and imipramine alters creatine kinase and mitochondrial respiratory chain activities in the rat brain. *Depress Res Treat* 2012; **2012**: 987397.

[3] Yonezawa T, Hasegawa S, Asai M, Ninomiya T, Sasaki T, Cha BY, et al. Harmine, a β-carboline alkaloid, inhibits osteoclast differentiation and bone resorption *in vitro* and *in vivo*. *Eur J Pharmacol* 2011; **650**(2-3): 511-518.

[4] Onishi Y, Oishi K, Kawano Y, Yamazaki Y. The harmala alkaloid harmine is a modulator of circadian Bmal1 transcription. *Biosci Rep* 2012; **32**(1): 45-52.

[5] Hamsa TP, Kuttan G. Harmine activates intrinsic and extrinsic pathways of apoptosis in B16F-10 melanoma. *Chin Med* 2011; **6**(1): 11.

[6] Frost D, Meechoovet B, Wang T, Gately S, Giorgetti M, Shcherbakova I, et al. β-carboline compounds, including harmine, inhibit DYRK1A and tau phosphorylation at multiple Alzheimer's disease-related sites. *PLoS One* 2011; **6**(5): e19264.

[7] Zaker F, Oody A, Arjmand A. A study on the antitumoral and differentiation effects of *Peganum harmala* derivatives in combination with ATRA on leukaemic cells. *Arch Pharm Res* 2007; **30**(7): 844-849.

[8] Farzin D, Haghparast A, Motaman S, Baryar F, Mansouri N. Effects of harmane and other β-carbolines on apomorphine-induced licking behavior in rat. *Pharmacol Biochem Behav* 2011; **98**(2): 215-219.

[9] Bouayad N, Rharrabe K, Lamhamdi M, Nourouti NG, Sayah F. Dietary effects of harmine, a β-carboline alkaloid, on development, energy reserves and a amylase activity of *Plodia interpunctella* Hübner [Lepidoptera: Pyralidae]. *Saudi Journal of Biological Sciences* 2011; **19**(1): 73-80.

[10] Beyer J, Drummer OH, Maurer HH. Analysis of toxic alkaloids in body samples. *Forensic Sci Int* 2009; **185**(1-3): 1-9.

[11] Herraiz T, González D, Ancín-Azpilicueta C, Arán VJ, Guillén H. beta-Carboline alkaloids in *Peganum harmala* and inhibition of human [MAO]. *Food Chem Toxicol* 2010; **48**(3): 839-845.

[12] Réus GZ, Stringari RB, de Souza B, Petronilho F, Dal-Pizzol F, Hallak JE, et al. Harmine and imipramine promote antioxidant activities in prefrontal cortex and hippocampus. *Oxid Med Cell Longev* 2010; **3**(5): 325-331.

[13] Begum S, Ali SN, Farhat, Hassan SI, Siddiqui BS. A simple, rapid and mild one pot synthesis of benzene ring acylated and demethylated analogues of harmine under solvent-free conditions. *Molecules* 2008; **13**(8): 1584-1598.

[14] Carpentier RG. Effects of harmala alkaloids on transmembrane potentials of guinea-pig papillary muscles. *Br J Pharmacol* 1982; **75**(1): 207-212.

[15] Cao R, Peng W, Chen H, Ma Y, Liu X, Hou X, et al. DNA binding properties of 9-substituted harmine derivatives. *Biochem Biophys Res Commun* 2005; **338**(3): 1557-1563.

[16] Zaidi MI, Coll I. Antifungal activity of harmine, $HgCl_2$ and their complex. *Sarhad J Agric* 2004; **20**(4): 623-626.

[17] Lala S, Pramanick S, Mukhopadhyay S, Bandyopadhyay S, Basu MK. Harmine: evaluation of its antileishmanial properties in various vesicular delivery systems. *J Drug Target* 2004; **12**(3): 165-175.

[18] Arshad N, Zitterl-Eglseer K, Hasnain S, Hess M. Effect of *Peganum harmala* or its beta-carboline alkaloids on certain antibiotic resistant strains of bacteria and protozoa from poultry. *Phytother Res* 2008; **22**(11): 1533-1538.

[19] Shahverdi AR, Monsef-Esfahani HR, Nickavar B, Bitarafan L, Khodaee S, Khoshakhlagh N. Antimicrobial activity and main chemical composition of two smoke condensates from *Peganum harmala* seeds. *Z Naturforsch C* 2005; **60**(9-10): 707-710.

[20] Rosenkranz V, Wink M. Alkaloids induce programmed cell death in bloodstream forms of trypanosomes [*Trypanosoma b. brucei*]. [Special Issue: Spiro compounds]. *Molecules* 2008; **13**(10): 2462-2473.

[21] Abe F, Nagafuji S, Yamauchi T, Okabe H, Maki J, Higo H, et al. Trypanocidal constituents in plants 1. Evaluation of some Mexican plants for their trypanocidal activity and active constituents in Guaco, roots of *Aristolochia taliscana*. *Biol Pharm Bull* 2002; **25**(9): 1188-1191.

[22] Fortunato JJ, Réus GZ, Kirsch TR, Stringari RB, Fries GR, Kapczinski F, et al. Chronic administration of harmine elicits antidepressant-like effects and increases BDNF levels in rat hippocampus. *J Neural Transm* 2010; **117**(10): 1131-1137.

[23] Fortunato JJ, Reus GZ, Kirsch TR, Stringari RB, Stertz L, Kapczinski F, et al. Acute harmine administration induces antidepressive-like effects and increases BDNF levels in the rat hippocampus. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; **33**(8): 1425-1430.

[24] Farzin D, Salimi E. Effects of harmane, norharmane and harmine on apomorphine-induced pecking behavior in chick. *Mazandaran Uni of Med Sciences* 2009; **19**(70): 747.

[25] Aricioglu-Kartal F, Kayir H, Tayfun Uzbay I. Effects of harman and harmine on naloxone-precipitated withdrawal syndrome in morphine-dependent rats. *Life Sci* 2003; **73**(18): 2363-2371.

[26] Frison G, Favretto D, Zancanaro F, Fazzin G, Ferrara SD. A case of beta-carboline alkaloid intoxication following ingestion of *Peganum harmala* seed extract. *Forensic Sci Int* 2008; **179**(2-3): e37-e43.

[27] Noll C, Planque C, Ripoll C, Guedj F, Diez A, Ducros V, et al. DYRK1A, a novel determinant of the methionine-homocysteine cycle in different mouse models overexpressing this Down-syndrome-associated kinase. *PLoS One* 2009; **4**(10): e7540.

[28] Lee K. Glutathione S-transferase activities in phytophagous insects: induction and inhibition by plant phototoxins and phenols. *Insect Biochem* 1991; **21**(4): 353-361.

[29] Lee K, Berenbaum MR. Action of antioxidant enzymes and cytochrome P-450 monooxygenases in the cabbage looper in response to plant phototoxins. *Arch Insect Biochem Physiol* 1989; **10**(2): 151-162.

[30] Adayev T, Wegiel J, Hwang YW. Harmine is an ATP-competitive inhibitor for dual-specificity tyrosine phosphorylation-regulated kinase 1A [Dyrk1A]. *Arch Biochem Biophys* 2011; **507**(2): 212-218.

[31] Göckler N, Jofre G, Papadopoulos C, Soppa U, Tejedor FJ, Becker W. Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation. *FEBS J* 2009; **276**(21): 6324-6237.

[32] Bartholome A, Kampkötter A, Tanner S, Sies H, Klotz LO. Epigallocatechin gallate-induced modulation of FoxO signaling in mammalian cells and *C. elegans*: FoxO stimulation is masked via PI3K/Akt activation by hydrogen peroxide formed in cell culture. *Arch Biochem Biophys* 2010; **501**(1): 58-64.

[33] Yu SJ. Allelochemical induction of hormone-metabolizing microsomal monooxygenases in the fall armyworm. *Zool Stud* 2000; **39**(3): 243-249.

[34] Zaidi MI, Gul A. Cytotoxicity studies of harmaline, harmine, metal salt and their complexes. *Sarhad J Agr* 2005; **21**(3): 477-479.

[35] Boeira JM, da Silva J, Erdtmann B, Henriques JA. Genotoxic effects of the alkaloids harman and harmine assessed by comet assay and chromosome aberration test in mammalian cells *in vitro*. *Pharmacol Toxicol* 2001; **89**(6): 287-294.

[36] Boeira JM, Viana AF, Picada JN, Henriques JAP. Genotoxic and recombinogenic activities of the two beta-carboline alkaloids harman and harmine in *Saccharomyces cerevisiae*. *Mutat Res-Fund Mol M* 2002; **500**(1-2): 39-48.

[37] Reza VRM, Abbas H. Cytotoxicity and antimicrobial activity of harman alkaloids. *J Pharmacol Toxicol* 2007; **2**(7): 677-680.

[38] Hamsa TP, Kuttan G. Harmine inhibits tumour specific neo-vessel formation by regulating VEGF, MMP, TIMP and pro-inflammatory mediators both *in vivo* and *in vitro*. *Eur J Pharmacol* 2010; **649**(1-3): 64-73.

[39] Ma Y, Wink M. The beta-carboline alkaloid harmine inhibits BCRP and can reverse resistance to the anticancer drugs mitoxantrone and camptothecin in breast cancer cells. *Phytother Res* 2010; **24**(1): 146-149.

[40] Song Y, Kesuma D, Wang J, Deng Y, Duan J, Wang JH, et al. Specific inhibition of cyclin-dependent kinases and cell proliferation by harmine. *Biochem Biophys Res Commun* 2004; **317**(1): 128-132.

[41] Jahaniani F, Ebrahimi SA, Rahbar-Roshandel N, Mahmoudian M. Xanthomicrol is the main cytotoxic component of *Dracocephalum kotschyii* and a potential anti-cancer agent. *Phytochemistry* 2005; **66**(13): 1581-1592.

[42] Yamazaki Y, Kawano Y. Inhibitory effects of herbal alkaloids on the tumor necrosis factor-α and nitric oxide production in lipopolysaccharide-stimulated RAW264 macrophages. *Chem Pharm Bull (Tokyo)* 2011; **59**(3): 388-391.

[43] Gao XL, Bi DZ, Sun DJ, Miao AD. Pharmacokinetics of harmine intravenous emulsion in rats and mice. *Acta Pharm Sinic* 2000; **35**(3): 224-227.

[44] Kumar GS, Swamy BMV, Babu VLA, Sridhar Chandanam Rao TS, Tarakaram K. HPTLC estimation of harmine from the stem bark of *Symplocos racemosa* Roxb. *Asian J Chem* 2006; **18**(4): 2851-2855.

[45] Grice ID, Ferreira LA, Griffiths LR. Identification and simultaneous analysis of harmane, harmine, harmol, isovitexin, and vitexin in *Passiflora incarnata* extracts with a novel HPLC method. *J Liq Chrom Rel Technol* 2001; **24**(16): 2513-2523.

[46] Munir C, Zaidi MI, Ahmad Atta-ur-Rahman N. An easy rapid metal mediated method of isolation of harmine and harmaline from *Peganum harmala*. *Fitoterapia* 1995; **66**(1): 73-76.

[47] Gonzalo-Lumbreras R, Rosales-Conrado N, León-González ME, Pérez-Arribas LV, Polo-Díez LM. Capillary liquid chromatography with diode array and mass spectrometry detection for heterocyclic aromatic amine determination in ready-to-eat food treated with electron-beam irradiation. *J Chromatogr A* 2010; **1217**(43): 6778-6784.

[48] Pietsch J, Günther J, Henle T, Dressler J. Simultaneous determination of thirteen plant alkaloids in a human specimen by SPE and HPLC. *J Sep Sci* 2008; **31**(13): 2410-2416.

[49] Patel DK, Laloo D, Kumar R, Hemalatha S. *Pedalium murex* Linn-An overview of its phytopharmacological aspects. *Asian Pac J Trop Med* 2011; **4**(9): 748-755.

[50] Patel DK, Kumar R, Prasad SK, Hemalatha S. Pharmacologically screened aphrodisiac plant-A review of current scientific literature. *Asian Pac J Trop Biomed* 2011; **1**(Suppl. 1): S131-S138.

[51] Patel DK, Prasad SK, Kumar R, Hemalatha S. An overview on antidiabetic medicinal plants having insulin mimetics property. *Asian Pac J Trop Biomed* 2012; **2**(4): 320-330.

[52] Patel DK, Kumar R, Laloo D, Hemalatha S. Diabetes mellitus: An overview on its pharmacological aspects and reported medicinal plants having andiabetic activity. *Asian Pac J Trop Biomed* 2012; **2**(5): 411-420.

[53] Patel DK, Prasad SK, Kumar R, Hemalatha S. Cataract: A major secondary complication of diabetes, its epidemiology and an overview on major medicinal plants screened for anticataract activity. *Asian Pac J Trop Dis* 2011; **1**(4): 323-329.