Alkaloids Derived from Tryptophan: Harmine and Related Alkaloids

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Abstract

Over 140 beta-carboline (Harmala) alkaloids are detected in bacteria, algae, fungi, various plant groups, food products, alcoholic beverages, tobacco smoke, marine bryozoa, insects, and animal tissue including human. Some of these alkaloids and their derivatives are synthesized chemically. Several natural and chemically formed alkaloids are biologically active, and they can be used as potent pharmaceutical drug for anticancer therapy, angiogenesis, Alzheimer's, free radical scavenger, *Leishmania*, and viruses Herpes, Influenza, Polio, and HIV.

Keywords

Angiogenic • antitumor • β-carboline • harmala alkaloids • harmine

Abbreviations

CNS	Central nervous system
CNTs–GCE	Carbon nanotubes–modified glassy carbon electrodes
GABA	Gamma-Aminobutyric acid
GC	Gas chromatography
HPLC	High-performance liquid chromatography
HPTLC	High-performance thin-layer chromatography
LC	Liquid chromatography
MAO	Monoamine oxidase
MS	Mass spectroscopy
TLC	Thin-layer chromatography

1 Synonyms

Harman: aribine, colloturine, loturine, passiflorin, 2-methyl-β-carboline, 3-methyl-4-carboline; Harmaline: harmidine, Harmalol, methyl ether, *O*-methyl-harmalol, 3,4-dihydroharmine; Harmine: telepathine, leucoharmine, yageine, banisterine; Tetrahydroharmine: elaeagnine, calligonine, leptaflorin

2 Introduction

β-carboline alkaloids are heterocyclic amines with a 9-*H*-pyrido[3,4,b] indole structure derived from amino acid tryptophan. Initially, they have been isolated from plant *Peganum harmala* L. (Syrian Rue) and are also known as harmala alkaloids. They are active constituents in hallucinogenic plants and have a long tradition in ethnopharmacology. Since then, they have been reported in variety of plant groups, fungi, microorganisms, and in animal tissue including human beings [1–3]. More than 140 different types of β-carbolines are reported so far in plant and animal system [4, 5]. Norharman, harmane, and harmine are also known as mammalian indole alkaloids because they are endogenously produced in human and animal tissues as a product of

secondary metabolism [6]. These compounds are also found in some medicinal plants [7]. During food production, processing, and storage, the chemical condensation between indoleamines and aldehydes or keto acids occurs naturally and results in formation of β-carbolines. Their presence is noted in well-cooked meat and fish and also in alcoholic beverages, tobacco smoke, and marijuana smoke [8]. They possess diverse biological properties due to their capability to bind to benzodiazepine or imidazoline receptors, such as hallucinogenic, tremorogenic, hypotensive or cardiovascular actions, and psychotropic properties.

3 Occurrence

β-carboline alkaloids are found mostly in plant system, but they also showed their presence in some animal tissue. In man, tetrahydro-beta-carboline (tetrahydronorharman), formed from tryptamine condensed with formaldehyde, occurs normally in plasma and is highly concentrated in platelets. After alcohol intake, its concentration is usually greatest at the time of hangover. These alkaloids may be found in particularly high concentrations (ng/g) in animal protein (i.e., meat). It is assumed that dietary sources were 50 times greater than endogenous sources [9]. Some β-carbolines, notably tryptoline and pinoline, are formed naturally in the human body [10].

β-carbolines are detected in bacteria, fungi, algae, and in plants belonging to bryophytes, pteridophytes, gymnosperm, angiosperms, and some specific marine organism (Table 19.1).

4 Phytochemistry

4.1 Physicochemical Characteristic

See Table 19.2.

4.2 Chemical Structures

See Fig. 19.1.

4.3 Extraction, Isolation, and Analysis

4.3.1 Extraction

Hundred grams of dried and powdered natural material (fruits, stem, or leaf) macerated with 250 ml of methanol at 50 °C in a water bath for 1 h., filter the extract with Whatman filter paper No. 1, and repeat the maceration of the material for four times. Combine the extract and evaporate to dryness. The residue was

Table 19.1 β-carboline alkaloids from some microorganism, plants, and animals

Sr. no.	Binomial name, family, and group	Common name	Part used	Type of β-carboline alkaloid	Reference
1	*Peganum harmala* L. Zygophyllaceae Dicotyledons	Harmal, Syrian rue	Seeds	Harman, harmine, harmaline, harmalol, harmidine, harmalidine	[11–13]
2	*Passiflora incarnata* L. Passifloraceae Dicotyledons	Maypop, passion flower	Aerial parts	Harmine, harman, norharman, harmol	[14, 15]
3	*Symplocos racemosa* Roxb. Symplocaceae Dicotyledons	Lodh tree, Lodh pathani	Bark	Harman	[16]
4	*Simira rubra* (Mart.) Steyerm. Rubiaceae Dicotyledons		Bark	Harman, harmine	[16]
5	*Banisteriopsis caapi* (Spr. ex Briesb.) Malpighiaceae Dicotyledons	Ayahuasca, caapi, yage	Aerial parts	Tetrahydroharmine, harmaline, harmine	[17]
6	*Elaeagnus angustifolia* L. Elaeagnaceae Dicotyledons	Russian silverberry	Bark	Tetrahydroharmine, harman	[18]
7	*Leptactina densiflora* Hook. f. Rubiaceae Dicotyledons	Leptactinia	Entire plant	Tetrahydroharmine	[19]
8	*Zygophyllum fabago* L. Zygophyllaceae Dicotyledons	Syrian bean-caper	Entire plant	Harmine	[20]
9	*Strychnos barnhartiana* Krukoff. Loganiaceae Dicotyledons		Leaves	Norharman	[21]

10	*Calligonum minimum* Lipski Polygonaceae Dicotyledons		Roots	Tetrahydroharmine	[7]
11	*Tribulus terrestris* L. Zygophyllaceae Dicotyledons	Puncture vine	Leaves	Harmaline, harmine, norharman, harman,	[22, 23]
12	*Grewia bicolor* Juss. Malvaceae Dicotyledons	White raisin	Aerial parts	Harman	[24]
13	*Uncaria attenuata* Korth.; *U. orientalis* Guill.; *U. canescens* Korth. Rubiaceae Dicotyledons		Leaves	Harman	[25]
14	*Oxalis tuberosa* Molina Oxalidaceae Dicotyledons	Oca	Tubers	Harmine, harmaline	[26]
15	*Festuca arundinacea* Schreb. Poaceae Monocotyledons	Tall fescue	Aerial parts	Norharman	[7, 16]
16	*Lolium perenne* L. Poaceae Monocotyledons	Ryegrass	Aerial parts	Norharman	[7, 16]
17	*Hypodematium squamuloso-pilosum* Ching Hypodematiaceae Pteridophyta	Fern	Aerial parts	1-acetyl-8-hydroxy-β-carboline; 1-acetyl-β-carboline	[27]
18	*Dichothrix baueriana* (Grun.) Bornet & Flahault Rivulariaceae Algae	Cyanobacteria	Biomass	7-chloro-9-mehtyl-β-carboline (bauerine A); 7,8-dichloro-9-mehtyl-β-carboline (bauerine B); 7,8-dichloro-1hydroxy-9-mehtyl-β-carboline (bauerine C)	[28]

(*continued*)

Table 19.1 (continued)

Sr. no.	Binomial name, family, and group	Common name	Part used	Type of β-carboline alkaloid	Reference
19	*Callophycus oppositifolius* (C. Agardh) P. C. Silva. Rhodophyceae Algae	red alga	Biomass	Tetrahydro-β-carbolines, 3-benzylamino-β-carboline (callophycin A)	[29]
20	*Nostoc* 78-12A Algae	blue green alga	Biomass	6-chloro-2-methyl-9 H-pyrido[3,4-b]indol-2-ium (nostocarboline)	[30]
21	*Nodularia harveyana* Thuret ex Bornet et Flahault; *Anabaena cylindrica* Lemmermann; *A. inaequalis* (Kützing) Bornet & Flahault; *Anabaenopsis siamensis* (Antarikanonda) Komárek & Anagnostidis; *Nostoc carneum* C. Agardh ex Bornet & Flahaul; *N. commune* Vaucher ex Bornet & Flahault Nostocaceae; *Phormidium foveolarum* Montagne ex Gomont Phormidiaceae; *Chroococcus Minutes* (Kützing) Nägeli Chroococaceae Chroococaceae	blue green algae	Biomass	Norharman	[31, 32]
22	*Streptomyces* spp. B1848; *Streptomyces* spp. B6005; *Flavobacterium* Bio215 Bacteria		Biomass	1-acetyle-β-carboline; perlolyrin; 1-[5-(hydroxymethyl)furan-2-yl]-9H-pyrido[3,4-b] indole-3-carboxylic acid (Flazin); 1-(9*H*-*β*-carbolin-1-yl)-3-hydroxy-propan-1-one	[5]
23	*Cribiceflina cribaria*	Marine bryozoa Ectoprocta	Biomass	1-vinyl-8-hydroxy-β-carboline; 1-Ethyl-4-methylsulfone-β-carboline; harman; I-ethyl-β-carboline	[33]
24	*Pterocella wesiculosa* Catenicellidae Ectoprocta	Marine bryozoa	Biomass	5-Bromo-8-methoxy-1-methyl-β-carboline	[34]

25	*Dragmacidon* sp. Axinellidae Demospongiae	Sea sponge	Body	Dragmacidonamine A; dragmacidonamine B	[35]
26	*Lignopsis spongiosum* Briareidae Anthozoa	Soft coral	Body	2-methyl-9H-pyrido [3,4*b*]-indole-3-carboxylic acid	[36]
27	*Nephila calviceps* Linn. Anthozoa Arthropoda	Golden orb web spider	Web of spider	1-(2-guanidinoethyl)-1,2,3,4-tetrahydro-6-hydroxymethyl)-β-carboline	[37]
28	7 species of butterflies Nymphalidae Insecta		Insect body	Harmine	[37]
29	*Rattus* sp. Muriade Mammalia	Rat		5-hydroxytryptamine; 5-methoxytryptamine	[38]
30	*Homo sapiens* Linn. Hominidae Mammalia	Human	Plasma and platelets	Tetrahydronorharman; harman	[38]

Table 19.2 Some characteristic features of selected β-carboline alkaloids

Alkaloid type	IUPAC name	Crystal	M. P.	Fluorescence in UV light	UV_{max} (nm)	Solubility
Harman $C_{12}H_{10}N_2$	1-methyl-9H-pyrido[3,4,b] indole	Orthorhombic	237–238 °C	Bright blue	234, 287, 347	Dilute acids
Harmaline $C_{13}H_{14}ON_2$	4,9-dihydro-7-methoxy-1-methyl-3 H-pyrido[3,4-b]indole	Orthorhombic bipyramidal prisms	229–231 °C	Blue	218, 260, 376	Dilute acids and hot ethanol
Harmine $C_{13}H_{12}ON_2$	7-methoxy-1-methyl-9 H-pyrido [3,4-b]-indole	Slender, orthorhombic prisms	261 °C	Blue	241, 301, 336	Slightly soluble in water, ethanol, ether, and chloroform
Norharman $C_{11}H_8N_2$	9 H-pyrido[3,4-b]indole	Orthorhombic	199–201 °C		281, 288, 339, 350	Ethanol, dilute acid
Harmol $C_{12}H_{12}ON_2$	1-methyl-2,9-dihydropyrido[3,4-b] indol-7-one	Slender needles	231 °C	Violet	303, 326, 338	Ethanol, dilute acid
Harmalol $C_{12}H_{12}N_2O$	1-Methyl-4,9-dihydro-3*H*-pyrido [3,4-*b*]indol-7-ol	Red needlelike crystals	211–212 °C	Green	330	Water, acetone, chloroform
Tetrahydroharmine $C_{13}H_{16}N_2O$	(1R)-7-methoxy-1-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole	Slender colorless needles	232–234 °C	Blue	225, 269, 296	Chloroform, ethyl acetate, ethanol, methanol

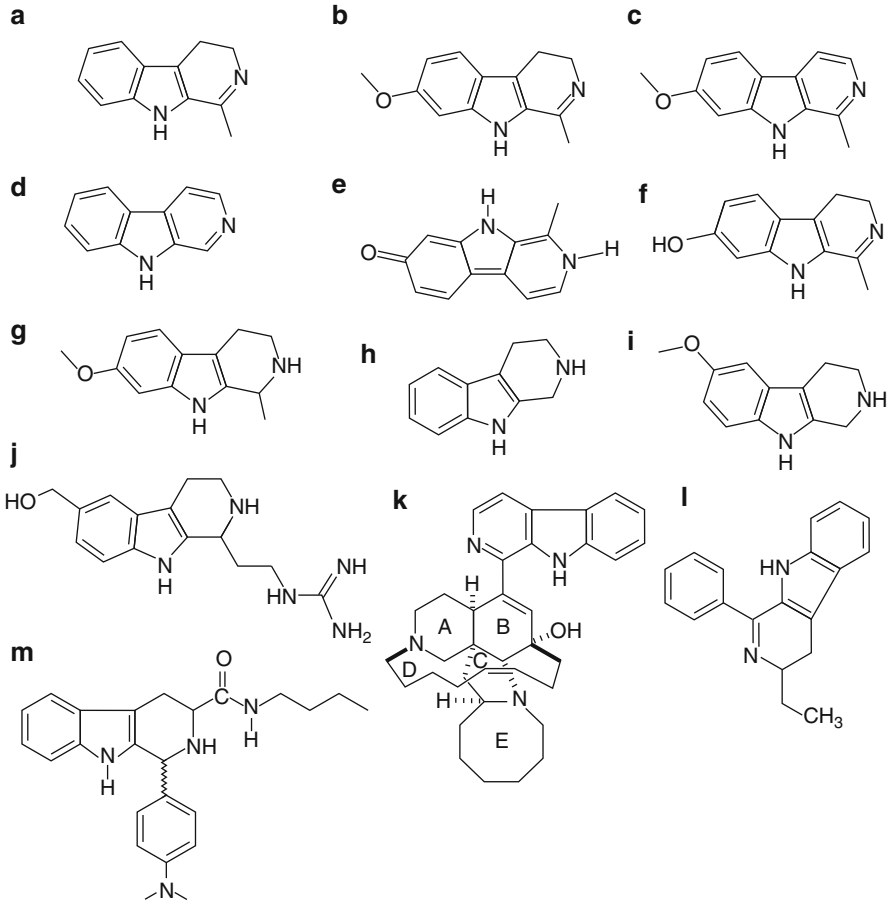

Fig. 19.1 Structure of some β-carbolines synthesized biologically and chemically: (1) From plant (**a**, **b**, **c**, **d**, **e**, **f**, and **g**); (2) From animals (**a**, **d**, **g**,**h**, **i**, **j**, and **k**); (3) Synthesized chemically (**l** and **m**). (**a**) Harman; (**b**) harmaline; (**c**) harmine; (**d**) norharman; (**e**) harmol; (**f**) harmalol; (**g**) tetrahydroharmine; (**h**) tryptoline; (**i**) pinoline; (**j**) 1-(2-guanidinoethyl)-1,2,3,4-tetrahydro-6-hydroxymethyl)-β-carboline [37]; (**k**) manzamine A [39]; (**l**) 3-ethyl-1-phenyl-4,9-dihydro-3*H*-beta-carboline; (**m**) *N*-butyl-1-(4-dimethylamino)phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxamide [40]

dissolved in 20 ml HCl (2%) and filtered through 0.45 μ filter. Wash the residue with HCl (2%) till colorless filtrate is obtained. Combine the filtrate and extract three times with equal volume of petroleum ether. The aqueous acid layer is basified (pH $>$ 10) with NH_4OH or NaOH and then extracts with equal volume of chloroform and repeat the extraction four times with chloroform. Wash the combine organic layer with water, dry the organic layer over anhydrous sodium sulfate, and remove the solvent under reduced

pressure to get the residue. The residue can be used after dissolution in methanol for detection and quantification using TLC, HPTLC, or HPLC method or adsorb the entire residue on a column grade silica gel. Place it on a column of grade silica gel. Carry out the gradient elution with increasing polarities of chloroform–methanol mixture. Monitor the column fractions with TLC/HPLC/HPTLC.

4.3.2 Isolation

For purification and separation, the final residue obtained by above-mentioned method is mixed with 50 ml of 3% v/v acetic acid and allowed to stand for 24 h with occasional stirring. Repeat it for at least three times. Combine the acid extract containing acetates of alkaloids and treat with NaCl (10 gm/100 ml extract), allow to cool and conversion of alkaloidal acetates to alkaloidal hydrochlorides precipitate (ppt). Discard the supernatant. Repeat the process, dissolve the ppt in warm water (50–60 °C), and add ammonia carefully till harmine begins to crystallize, filter, and separate harmine crystals. Add ammonia to filtrate and allow to precipitate harmaline. Wash the crystals and subject to purification or recrystallization [41].

4.3.3 Analysis

Selective and sensitive detection of β-carbolines is possible using HPLC methods in combination with UV, chemiluminescence, and fluorometry. Besides this, LC-MS and GC-MS are the techniques predominantly used for identification, separation, and quantitation of β-carbolines and tetrahydro-β-carbolines [13, 42]. These alkaloids are detected in foods and beverages by HPLC with electrochemical detection at carbon nanotubes–modified glassy carbon electrodes (CNTs–GCE) [43]. In the seeds of *Peganum harmala* L., the alkaloids harmol, harmalol, harmine, and harmaline were separated using a Metasil ODS column by isocratic elution with isopropyl alcohol:acetonitrile:water: formic acid (100:100:300:0.3) (v/v/v/v pH adjusted 8.6 with triethylamine) and detected at 330 nm [13]. These alkaloids can be detected by HPTLC method [44].

Simultaneous quantification of 11 compounds found in ayahuasca (A popular Amazonian botanical medicine and religious sacrament) has been achieved using direct injection/liquid chromatography- electrospray ionization (ESI)-selected reaction monitoring (SRM) - tandem mass spectrometry procedure [45, 46].

5 Biosynthesis

The β-carboline alkaloids are heterocyclic amines, biosynthesized from combination of five- and six-ringed (i.e., cyclic) carbon structures, containing an amine group. β-carboline is made up of planar tricyclic ring structures derived from L-tryptophan (i.e., α-aminoindole-3-propinoic acid), a neutral heterocyclic amino acid containing essentially an indole ring system. The shikimic acid

pathway converts the simple carbohydrate precursors phosphoenolpyruvate and erythrose-4-phosphate derived from glycolysis and pentose phosphate pathway, respectively, to aromatic amino acids (L-tryptophan). Decarboxylation of L-tryptophan yields tryptamine. The C-2 of indole nucleus is nucleophilic due to adjacent nitrogen atom which allows it to participate in a Mannich/Pictet–Spengler type reaction. These rearrangements enable a Schiff base derived from tryptamine to interact either with aldehyde or keto acid to yield β-carboline carboxylic acid which on oxidative decarboxylation gives rise to 1-methyl β-carboline. In formation of simple structures of β-carboline, keto acids are used, e.g., harman, harmaline, and elaeagnine. For formation of complex structures, the specific pathways used the aldehyde, e.g., ajmaline (terpenoid indole alkaloids). Hydroxylation followed by methylation of 1-methyl-β-carboline yields harmaline, while on reduction it yields elaeagnine, and upon mild oxidation produces harman. Oxidation of harmaline with loss of water molecule generates harmine while on reduction yield tetrahydroharmine. The demethylation of harmine gives rise to the alkaloid harmalol. Harmaline on condensation, oxidation, and decarboxylation yields to norharmine (Fig. 19.2).

6 Chemical Synthesis

Several beta-carboline alkaloids and their derivatives are chemically synthesized through the Pictet–Spengler reaction using tryptophan, its derivatives, and oxidation of $K_2Cr_2O_7$ by a sequential one-pot synthesis method [47]. There are some other methods reported for the chemical synthesis of β-carboline alkaloids [48–51].

$$\begin{aligned}&\beta\text{-phenyltryptamine} + \mathrm{HCOOH} \rightarrow \text{N-formyl-}\beta\text{-phenyltryptamine}\\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\downarrow +\mathrm{POCl_3}\\ &\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\text{4-Phenyl-3, 4-dihydro-}\beta\text{-carboline}(5)(\text{monohydrate})\end{aligned}$$

7 Biological Activities

β-carboline alkaloids are widespread in plants and animals. Numerous reports investigated the effects of β-carboline alkaloids on the central nervous system (CNS). However, recent interest in this alkaloid and its derivatives has been focused on their potent antitumor, anticancer, antiviral, antimicrobial, antioxidant, antiparasitic, and several other biological activities [52]. The chemical analysis of plants *Banisteriopsis caapi* used in preparation of ancient drug "ayahuasca" showed that the active chemical constituent named telepathine was found to be identical to a chemical already isolated from *Peganum harmala* and was given the name harmaline. Later, it is well established that the β-carbolines are component of

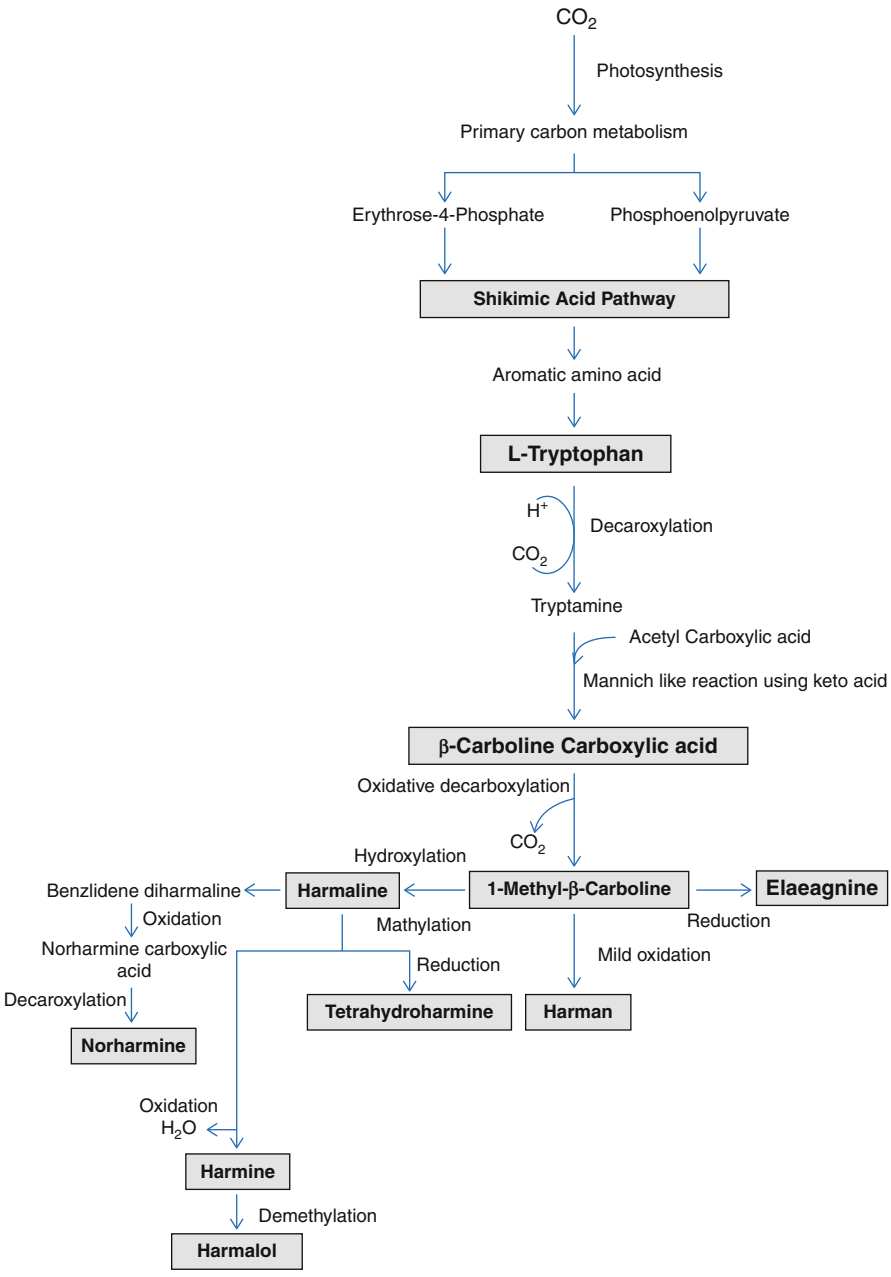

Fig. 19.2 Outline of harmala alkaloid biosynthesis

some medicinal plants, such as *Peganum harmala* (Zygophyllaceae), *Passiflora incarnata* (Passifloraceae), and *Banisteriopsis caapi* (Malpighiaceae) (details are given in Table 19.1).

Beta carboline has biochemical, neurophysiological and the pharmacological effects in animals and man. They participate in several actions, including inhibition of MAO-A, 5-HT uptake, general inhibiton of Na^+ dependent transports, act as neuromodulators and some may have an endocrinological function [53].

7.1 Interaction with DNA and RNA

Some of the mutagenic and carcinogenic effects of β-carboline alkaloids have been studied in prokaryotic and eukaryotic cells related to their ability to intercalate into DNA [54, 55]. The β-carboline derivatives inhibit DNA topoisomerases and interfere with DNA synthesis. Harmine-, harmaline-, harman-, and norharman-inhibited DNA excisions repair directly or indirectly and lead to altered DNA replication fidelity and enzymatic activities in DNA-repair processes [56, 57]. These alkaloids consequently enhance UV or chemically induced mutagenesis [58]. Harman- and harmine-induced chromosome aberrations in Chinese hamster ovary cells after treatment with the clastogens mitomycin C and UV light [59] while in human neuroblastoma SH-SY5Y cells harman and norharman induced apoptosis as well as necrosis [60]. Aminophenylnorharman, a newly identified beta-carboline alkaloid induced sister chromatid exchange and chromosome aberrations in cultured Chinese hamster lung cells. The different types of β-carboline alkaloids showed variation in affinity to bind DNA, and it is in the order of harmine > harmalol > harmaline > harmane > tryptoline [61]. These alkaloids also bind with yeast RNA [62].

7.2 Interaction with Enzymatic Systems and Receptors

The activity of certain enzymes is inhibited in the presence of beta-carboline alkaloids. The alkaloids interact with neurotransmitter systems such as opiate, GABA, muscarinic, and cholinergic [59]. Inhibition of human DNA Topoisomerase I activity was observed with the seed extract of *Peganum harmala* L. in which harmine, harman, and harmaline are the dominating components [63]. Harmines were found as potent inhibitors of cyclin-dependent kinases [64, 65] and IkappaB kinase. Norharman acts as an inhibitor of the heme containing cytochrome (P450 CYP) related enzymes [66]. Different β-carboline alkaloids show bindings to several receptors like serotonin, benzodiazepines, 5-hydroxytryptamine, dopamine, and imidazoline [67, 68].

Recent results suggest that β-carboline alkaloids may exhibit antidepressant effects [69, 70], probably linked to its inhibitory actions on MAO [71, 72]. This might be the reason for psychopharmacological and toxicological effects of

seed and root extracts of *P. harmala* containing β-carbolines and could be the basis for its purported antidepressant actions [73].

7.3 Neurotoxic Effects

Administration of β-carboline alkaloids to human being and a wide variety of laboratory animals produces an intense and generalized action tremor [74]. Harmane is a potent, tremor-producing β-carboline alkaloid and is used in epidemiological studies. It is one of the most abundant of all dietary heterocyclic amines, and human exposure to harmane through diet is greater than that of other heterocyclic amines [9, 67]. Due to its high-lipid solubility, harmane accumulates in brain tissue [75]. It provides the rationale for an in-depth scrutiny of their potential role in the etiology of essential tremor (ET), the most common tremor disorder [76]. β-carboline alkaloids are highly neurotoxic.

7.4 Antitumor Activities

β-carboline alkaloids synthesizing plants such as *P. harmala*, *Banisteriopsis caapi*, and *Passiflora incarnata* have been used as folk medicine in anticancer therapy. Recently, they have drawn attention because of their antitumor and anti-angiogenic activity. Angiogenesis is the physiological process responsible for vasculogenesis and formation of new blood vessels [77]. However, it is also a fundamental step in the transition of tumors from a dormant to a malignant state.

In vivo, anti-angiogenic activity on B16F-10 melanoma cells showed that harmine acts as strong angiogenic inhibitor which significantly decreased pro-angiogenic factors such as vascular endothelial growth factor, nitric oxide, and pro-inflammatory cytokines. At the same time, it increased antitumor factors [78]. β-carboline alkaloids (Callophycin A) show promising antitumor activity against a panel of mammalian cell lines [52, 79, 80]. Several β-carboline derivatives designed and chemically synthesized with various substituents on harmine to produce lower toxicity drug but effective against tumor. However, the structure–activity relationships (SAR) showed that the antitumor activity and acute toxicity as well as neurotoxic effect of β-carboline derivatives are substituent-dependant. Chemically synthesized 1-phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and methyl 1-phenyl-β-carboline-3-carboxylate are potent compounds with better cytotoxicity against insect cultured Sf9 cell line [81].

7.5 Antiviral Activities

The β-carboline alkaloids and their derivatives are emerging as potent antiviral agents. Eudistomins C, D, E, H, I, K, L, N, and Q, manzamine A, and 8-hydroxymanzamine

A were effective against herpes simplex virus-1 (HSV-1and II) [82, 83]. Eudistomin K sulfoxide and eudistomin K have high activities against polio vaccine type-1 virus. Platinum (II) and palladium (II) complexes of harmaline, harmalol, harmine, and harman and (−)-Debromoeudistomin K were also observed to exhibit antiviral activities against influenza virus (A and B) and herpes virus [84]. Recently, harman and its derivatives were found to possess anti-HIV activities against human peripheral blood mononuclear (PBM) cells [85].

7.6 Antimicrobial Activities

Currently, Eudistomins and its derivatives showed antimicrobial activity against *Saccharomyces cerevisiae*, *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans* [86, 87]. β-carboline alkaloids from marine bryozoan *Cribricellina cribraria* showed antimicrobial activities against *Pseudomonas aeruginosa* and *Escherichia coli*, *Bacillus subtilis* and fungi *Candida albicans*, *Trichophyton mentagrophytes*, and *Cladisporum resinae* [33]. The antimicrobial activity increased on application of β-carboline alkaloids as binary mixtures against *Proteus vulgaris*, *Bacillus subtilis*, and *Candida albicans* [88]. The antibacterial activity was higher with harmane as compared to harmaline, harmalol, and harmine [89].

7.7 Antiparasitic Activity

The most common β-carboline alkaloids harmine, harmane, and harmaline possess antiparasitic activities against *Leishmania mexicana* [90] and displayed antileishmanial activity toward the intracellular amastigote form of *Leishmania* [91]. Some β-carboline alkaloids are active against epimastigotes of *Trypanosoma* species [56, 92].

7.8 Antithrombotic Activity

The substituent on the β-carboline alkaloids changes the polarity, charge, molecular size, and spatial arrangement which might be the key factors in influencing their biological activity. Antithrombotic activity was detected in phenolic tetrahydro-β-carboline conjugates, perlolyrine, and its analogue [93, 94].

7.9 Antioxidant Activity

It has been reported that β-carbolines and tetrahydro-β-carbolines are potent antioxidants and may be useful for the prevention of diseases associated with oxidative damage [95]. Harmane, harmaline, harmalol, and their peptide conjugates designed and synthesized possess free radical scavenging activity [95, 96].

7.10 Antiplasmodial Activity

Harmine and harmaline showed a moderate in vitro antiplasmodial activity against *Plasmodium falciparum* [97].

7.11 Other Activities

β-carbolines also help in improving object recognition memory and stimulating insulin secretion [98]. They are useful in treatment of hypopigmentation-related disorders such as vitiligo as they induce cellular melanin biosynthesis [99]. Some of the chemically synthesized β-carboline showed better insecticidal activity. Harmine, harmaline, harmol, and harman showed good inhibitory activities against acetylcholinesterase inhibitors (AChE), therefore, they can form the basis of the newest drugs for the treatment of Alzheimer's disease [100]. Recently, it was reported that β-carbolines induce apoptosis by caspase-8 activation in carcinoma cells and function as an anti-inflammatory compound [101]. Pinoline formed naturally in the human body is implicated along with melatonin in the role of the pineal gland in regulating the sleep–wake cycle.

8 In Vitro Production

The alkaloids harmine, harmaline, harman, and harmalol have been detected in callus and cell culture of *Peganum harmala* [102] and *Tribulus terrestris* [23]. The hairy root induction was achieved in *P. harmala* with the help of *Agrobacterium rhizogene*. Harmine is the major alkaloid found in the normal root and hairy root culture. The alkaloids content were enhanced in hairy root culture of *P. harmala* by using the elicitor H_2O_2 and biosynthetic precursor, tryptophan [103]. The somatic embryoids of *Tribulus terrestris* are one of the best sources of Harmala alkaloids [23].

9 Conclusion

Certain β-carbolines are very toxic or precursors of mutagens while others are necessary to maintain normal metabolism or to recover from disorder. Human beings and animals are frequently exposed to beta-carboline alkaloids as they produced in well-cooked food, tobacco smoke, and hallucinogenic beverages. These metabolites are also synthesized endogenously in animal tissue. Some of the medicinal plants particularly *Peganum harmala*, *Passiflora incarnata*, and *Banisteriopsis caapi* are very rich sources of harmala alkaloids and are used in folk medicine for their antispasmodic, anti-jaundice, anti-lumbago, anti-inflammation agent, anticancer, antimalarial, and sedative properties and in the treatment of asthma. The world famous ayahuasca, a narcotic drug, is prepared using *Banisteriopsis* sp. and contains harmala alkaloids. These alkaloids are widely

distributed in plants and animals. They are biosynthesized from tryptophan and pyruvate or acetate precursors. Some of these alkaloids and their derivatives are synthesized chemically. Enhanced production of some alkaloids occurs in cell and hairy root culture of *Peganum harmala* and somatic embryoids of *Tribulus terrestris*. Literature survey indicates that the beta-carboline alkaloid had extensive biochemical activities and multiple pharmacological effects. Taking all those reports together, it is revealed that some beta-carbolines and their derivatives from natural source and are chemically synthesized can be an important basis for the design and synthesis of potent pharmaceutical drug.

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