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Chapter 6

LC-HRMS for the Identification of β-Carboline and Canthinone Alkaloids Isolated from Natural Sources

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Abstract

β-carboline and canthinone alkaloids are widely distributed in the Angiosperms. Due to their diverse biological activities, the structures of these alkaloids have been used as important models for the synthesis of novel therapeutic drugs. Combining high-performance liquid chromatography (HPLC) with high-resolution mass spectrometry (HRMS) has provided a valuable tool in the analysis of these alkaloids in, for example, plants, insects, marine creatures, human tissues and body fluids. In this review, we summarized the main β-carboline and canthinone alkaloids studied by liquid chromatography high-resolution mass spectrometry (LC-HRMS) associated with mass analyzers, molecular weight information, mass fragmentation and biological activities, presenting an overview of increasing interest for carboline alkaloids study by LC-HRMS.

Keywords: chromatography, indole, mass analyzer, fragmentogram, biological activity, body samples

1. Introduction

Since ancient times, alkaloids have been used as medicine and in folk medicine for the treatment of different diseases. β-Carboline alkaloids are a group of natural indole alkaloids with different degrees of aromaticity widely distributed in the Angiosperms [1–61]. Canthinones

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are β-carboline alkaloids that have an additional ring-fusion. Analysis of these alkaloids may be realized by combination of liquid chromatography-high-resolution mass spectrometry (LC-HRMS/MS) to produce information about metabolites contained in complex natural source samples. The LC-HRMS is commonly used as choice technique to analyze and elucidate β-carboline and canthinone alkaloids of the extract mixture and that fact will be approached in this review together with other topics described below.

2. Source of β-carboline and canthinone alkaloids

In the plant kingdom, β-carboline and canthinone alkaloids are mainly found in Angiosperms, predominantly in Simaroubaceae, Rubiaceae, Rutaceae, Apocynaceae, Amaranthaceae, Annonaceae, Zygophyllaceae and Passifloraceae families [1–61]. **Table 1** shows the alkaloids of these two classes and their natural sources. These alkaloids have been obtained mainly in the studies of isolation of chemical constituents from a natural source, chromatographic LC-HRMS analyses and biological studies.

Alkaloid	Species	Refs.
Annomontine	Annonaceae: *Annona foetida* Mart., *A. montana* Macf., *A. purpurea* Moc & Sessé ex Dunal, *A. reticulata* L.	[1–3]
Brunneins A–C	Cortinariaceae: *Cortinarius brunneus*(Pers.) Fr.	[4]
Canthin-2,6-dione	Simaroubaceae: *Simaba multiflora* A. Juss., *S. polyphylla* (Cavalcante) W.W. Thomas	[5, 6]
Canthin-6-one	Amaranthaceae: *Aerva lanata* (L.) A.L. Juss. ex Schultes; Rutaceae: *Fagara mayu* (Bert.) Engl., *F. viridis* A. Chev., *F. zanthoxyloides* Lam., *Pentaceras australis* Hook. F., *Phellodendron amurense* Rup., *Zanthoxylum belizense* Lundell, *Z. chiloperone* var. *angustifolium* (Engl.), *Z. coreanum* Nakai, *Z. dipetalum* H. Mann, *Z. elephantiasis* Macfad., *Z. flavum* Vahl, *Z. ovalifolium* Tutcher, *Z. suberosum* C.T. White; Simaroubaceae: *Ailanthus altissima* Swingle, *A. excelsa* Roxb., *Brucea antidysenterica* J.F. Mill., *Eurycoma harmandiana* Pierre, *E. longifolia* Jack, *Hannoa chlorantha* Engl. & Gilg., *H. klaineana* Pierre & Engl., *Odyendea gabonensis* (Pierre) Engler, *Picrasma crenata* Engl. in Engl. & Prantl	[6–24]
Canthin-6-one-3-N-oxide	Rutaceae: *Zanthoxylum chiloperone* var. *angustifolium* (Engl.); Simaroubaceae: *Ailanthus altissima* Swingle, *Eurycoma harmandiana* Pierre, *Hannoa chlorantha* Engl. & Gilg., *Simarouba berteroana* Krug & Urban	[6, 8, 11, 13, 14, 17, 25]
Canthin-6-one-9-methoxy-5-*O*-β-D-glucopyranoside	Simaroubaceae: *Simarouba berteroana* Krug & Urban	[25]
β-Carboline-1-propionic acid	Amaranthaceae: *Aerva lanata* (L.) A.L. Juss. ex Schultes; Rutaceae: *Zanthoxylum chiloperone* var. *angustifolium* (Engl.); Simaroubaceae: *Eurycoma harmandiana* Pierre, *Simarouba berteroana* Krug & Urban	[9, 17, 25]
(E)-O-(6′)-Cinnamoyl-4″-hydroxy-3″, 5″-dimethoxy-lyaloside	Rubiaceae: *Psychotria suterella* Müll. Arg., *P. laciniata* Vell.	[26–28]
Deppeaninol	Rubiaceae: *Deppea blumenaviensis* (K. Schum.) Lorence	[29]
4,5-Dihydrocanthin-6-one	Simaroubaceae: *Ailanthus altissima* Swingle	[21]

Alkaloid	Species	Refs.
1,11-Dimethoxycanthin-6-one	Simaroubaceae: *Brucea antidysenterica* J.F. Mill., *Picrasma quassioides* (D. Don) Benn., *Soulamea pancheri* Brongn. & Gris	[21]
4,5-Dimethoxycanthin-6-one	Simaroubaceae: *Odyendea gabonensis* (Pierre) Engler; *Picrasma quassioides* (D. Don) Benn., *Picrolemma granatensis*, *Quassia africana* (Baill.) Baill.	[21, 22, 30–33]
5,9-Dimethoxycanthin-6-one	Simaroubaceae: *Eurycoma longifolia* Jack	[24]
9,10-Dimethoxycanthin-6-one	Simaroubaceae: *Eurycoma harmandiana* Pierre	[17]
Eudistomin G, H, I, P, R, S, T	Polycitoridae: *Eudistoma olivaceum* Van Name	[34]
Eurycomine E	Simaroubaceae: *Picrasma quassioides* (D. Don) Benn.,	[35]
11-O-β-D-Glucopyranosylcanthin-6-one	Simaroubaceae: *Eurycoma longifolia* Jack	[24]
10-O-β-D-Glucopyranosyloxycanthin-6-one	Amaranthaceae: *Aerva lanata* (L.) A.L. Juss. ex Schultes	[9]
1-(2-Guanidinoethyl)-1,2,3,4-tetrahydro-3-(hydroxymethyl)-β-carboline	Nephilidae: *Nephila clavipes* L.	[23]
Harmaline	Malvaceae: *Grewia bicolor* Juss.; Passifloraceae: *Passiflora edulis* f. *flavicarpa* O. Deg., *P. incarnata* L.; Zygophyllaceae: *Peganum harmala* L. *Tribulus terrestris* L.	[36–39]
Harmalol	Zygophyllaceae: *Peganum harmala* L.	[36]
Harmane	Ciidae: *Coriolus maximus* (Mont.) Murrill Malvaceae: *Grewia bicolor* Juss; Passifloraceae: *Passiflora edulis* f. *flavicarpa* O. Deg., *P. incarnata* L.; Tricholomataceae: *Hygrophorus eburneus* (Bull.) Fr.; Zygophyllaceae: *Tribulus terrestris* L.	[4, 37–39]
Harmicine	Apocynaceae: *Kopsia griffithii* King & Gamble	[40, 41]
Harmine	Malpighiaceae: *Banisteriopsis caapi* (Spruce ex Griseb.) Morton; Malvaceae: *Grewia bicolor* Juss.; Passifloraceae: *Passiflora edulis* f. *flavicarpa* O. Deg., *P. incarnata* L.; Zygophyllaceae: *Tribulus terrestris* L.; *Peganum harmala* L.	[36–39]
Harmol	Passifloraceae: *Passiflora edulis* f. *flavicarpa* O. Deg.; Zygophyllaceae: *Peganum harmala* L.	[36, 37]
N-Hydroxyannomontine	Annonaceae: *Annona foetida* Mart.	[1, 2]
10-Hydroxy-antirhine	Apocynaceae: *Ochrosia alyxioidis* Guillaumin; Rubiaceae: *Psychotria prunifolia* (Kunth) Steyerm.	[29]
10-Hydroxy-antirhine N-oxide	Rubiaceae: *Psychotria prunifolia*(Kunth) Steyerm.	[29]
1-Hydroxycanthin-6-one	Simaroubaceae: *Ailanthus altissima* Swingle, *Hannoa chlorantha* Engl. & Gilg.	[8, 11]
11-Hydroxycanthin-6-one	Simaroubaceae: *Ailanthus altissima* Swingle	[18]
8-Hydroxycanthin-6-one	Simaroubaceae: *Hannoa chlorantha* Engl. & Gilg., *Odyendea gabonensis* (Pierre) Engler	[11, 22]
9-Hydroxycanthin-6-one	Simaroubaceae: *Ailanthus altissima* Swingle, *Eurycoma harmandiana* Pierre, *Picrolemma granatensis*, *Simarouba berteroana* Krug & Urban	[17, 18, 25, 31]

Alkaloid	Species	Refs.
10-Hydroxycanthin-6-one (aervine)	Amaranthaceae: *Aerva lanata* (L.) A.L. Juss. ex Schultes; Simaroubaceae: *Ailanthus altissima* Swingle; *Hannoa chlorantha* Engl. & Gilg.	[9, 11, 18]
11-Hydroxycanthin-6-one-N-oxide	Simaroubaceae: *Simarouba berteroana* Krug & Urban	[25]
9-Hydroxycanthin-6-one-N-oxide	Simaroubaceae: *S. berteroana*	[25]
(R)-5-(1-Hydroxyethyl)-canthine-6-one	Simaroubaceae: *Ailanthus altissima* Swingle	[18]
10-hydroxy-iso-deppeaninol	Rubiaceae: *Psychotria prunifolia* (Kunth) Steyerm.	[29]
1-Hydroxy-11-methoxycanthin-6-one	Simaroubaceae: *Eurycoma longifolia* Jack	[24]
10-Hydroxy-9-methoxycanthin-6-one	Simaroubaceae: *E. longifolia*	[21, 24]
11-Hydroxy-1-methoxycanthin-6-one	Simaroubaceae: *E. longifolia*	[21]
11-Hydroxy-10-methoxycanthin-6-one	Simaroubaceae: *E. longifolia*	[24]
5-Hydroxy-4-methoxycanthin-6-one (nigakinone)	Simaroubaceae: *Picrasma excelsa* (SW.) Planch. *Picrasma quassioides* (D. Don) Benn.	[21, 30, 32, 33, 42, 43]
8-Hydroxy-9-methoxycanthin-6-one	Simaroubaceae: *Picrolemma granatensis*, *Simarouba berteroana* Krug & Urban	[25, 31]
8-Hydroxymanzamine A	Petrosiidae: *Acanthostrongylophora ingens* (Thiele); Phloeodictyidae: *Pachypellina* sp.	[44, 45]
6-Hydroxymetatacarbolines A, B, C, D, E, F, G, H, I	Mycenaceae: *Mycena metata* (Fr.) Kumm.	[4]
1-(Hydroxymethyl)-3-(2-hydroxypropan-2-yl)-2-(5-methoxy-9H-β-carbolin-1-yl) cyclopentanol	Rubiaceae: *Galianthe thalictroides* (K. Schum.) E.L. Cabral	[46]
Isovallesiachotamine	Rubiaceae: *Chimarrhis turbinata* DC., *Palicourea rigida* Kunth, *Psychotria bahiensis* DC., *P. suterella* Müll. Arg., *P. laciniata* Vell.	[27]
Lyaloside	Rubiaceae: *Ophiorrhiza japonica* Blume, *Psychotria suterella* Müll. Arg., *P. laciniata* Vell., *Pauridiantha lyalli* (Baker) Bremek., *Uncaria tomentosa* (Willd. ex Schult.) DC., *Palicourea adusta* Standley	[26–28]
Manzamine A	Petrosiidae: *Acanthostrongylophora ingens* (Thiele)	[44]
Metatacarbolines A, B, C, D, E, F, G	Mycenaceae: *Mycena metata* (Fr.) Kumm.	[4]
Methoxyannomontine	Annonaceae: *Annona impressivenia* Safford, *A. Montana* Macf., *A. reticulate* L.; Lauraceae: *Neolitsea Konishii* (H.) Kan & Sas	[2]
3-Methoxycanthin-2,6-dione	Simaroubaceae: *Simaba cuspidata* Spruce ex Engl., S. *multiflora* A. Juss.	[21, 47]
1-Methoxycanthin-6-one	Simaroubaceae: *Ailanthus altissima* Swingle, *Hannoa chlorantha* Engl. & Gilg.	[8, 11]
10-Methoxycanthin-6-one (methylaervine)	Amaranthaceae: *Aerva lanata* (L.) A.L. Juss. ex Schultes	[9]

Alkaloid	Species	Refs.
4-Methoxycanthin-6-one	Amaranthaceae: *Charpentiera obovata* Gaudich.	[6, 48]
5-Methoxycanthin-6-one	Rutaceae: *Zanthoxylum caribaeum* Lam., *Z. chiloperone* var. *angustifolium*(Engl.), Simaroubaceae: *Leitneria floridana* Chapm., *Odyendea gabonensis* (Pierre) Engler	[6, 10, 12–14, 22, 49]
9-Methoxycanthin-6-one	Simaroubaceae: *Eurycoma longifolia* Jack, *Picrolemma granatensis*, *Simaba polyphylla* (Cavalcante) W.W. Thomas, *Simarouba berteroana* Krug & Urban	[5, 17, 25, 31, 50]
9-Methoxycanthin-6-one-3-N-oxide	Simaroubaceae: *Picrolemma granatensis*	[31]
7-Methoxy-β-carboline-1-propionic acid	Simaroubaceae: *Eurycoma harmandiana* Pierre	[17]
1-Methoxycarbonyl-β-carboline	Simaroubaceae: *Picrasma quassioides* (D. Don) Benn.	[42]
9-Methoxy-3-methylcanthin-5,6-dione	Simaroubaceae: *Eurycoma longifolia* Jack	[50]
1-Methoxymethyl-β-carboline	Simaroubaceae: *E. longifolia*	[24]
3-Methylcanthin-2,6-dione	Simaroubaceae: *Picrasma quassioides* (D. Don) Benn.	[30, 42]
N-Methyltetrahydro-β-carboline	Amaranthaceae: *Arthrophytum leptocladum* M. Pop. ex Iljin, *Cyathobasis fruticulosa* (Bunge) Aellen, *Hammada leptoclada* Iljin; Elaeagnaceae: *Elaeagnus angustifolia* L.; Leguminosae: *Acacia simplicifolia* (L.f.) Schinz & Guillaumin, *Anadenanthera peregrina*(L.) Speg.; Malpighiaceae: *Banisteriopsis rusbyana* (Nied.) Morton; Myristicaceae: *Gymnacranthera paniculata* (A.DC.) Warb., *Virola sebifera* Aubl., *Virola theiodora* (Spruce ex Benth. Warb.; Phyllanthaceae: *Flueggea microcarpa* Blume; Poaceae: *Phalaris aquatica* L.; Rubiaceae: *Psychotria carthagenensis* Jacq.; *Psychotria viridis* Ruiz & Pav.; Ochnaceae: *Testulea gabonensis* Pellegr.	[8, 51, 52]
Mitragynine	Rubiaceae: *Mitragyna speciosa* Korth	[53]
Norharmane	Tricholomataceae: *Hygrophorus eburneus* (Bull.) Fr.	[54]
14-Oxoprunifoleine	Rubiaceae: *Psychotria prunifolia* (Kunth) Steyerm.	[29, 55]
Paymantheine	Rubiaceae: *Mitragyna speciosa* Korth	[53]
Picrasidine L (3-methylcanthin-5,6-dione)	Simaroubaceae: *Eurycoma longifólia* Jack, *Picrasma quassioides* (D. Don) Benn., *Quassia amara* L.	[21, 50]
Picrasidine N, M, U, W, X, Y	Simaroubaceae: *Picrasma quassioides* (D. Don) Benn.	[21]
Picrasidine O	Simaroubaceae: *Eurycomma longifólia* Jack, *Picrasma quassioides* (D. Don) Benn.	[21, 35]
Picrasidine P, V	Simaroubaceae: *P. quassioides*	[56]
Picrasidine Q (4-hydroxy-5-methoxycanthin-6-one)	Simaroubaceae: *P. quassioides*	[33]
Psychollatine	Rubiaceae: *Psychotria umbellate* Thonn.	[27]
Reserpine	Apocynaceae: *Rauvolfia hookeri* S.R. Sriniv. & Chithra, *R. micrantha* Hook. f., *R. serpentina* (L.) Benth. ex Kurz, *R.tetraphylla* L., *R. verticillata* (Lour.) Baill., *R. vomitoria* Afzel	[57]
Speciogynine	Rubiaceae: *M. speciosa*	[53]
Strictosamide	Rubiaceae: *Psychotria nuda* (Cham. et Schltdl) Wawra, *P. suterella* Müll. Arg., *P. laciniata V*ell., *P. prunifolia* (Kunth) Steyerm.	[27, 29, 55, 58]

Alkaloid	Species	Refs.
Strictosidinic acid	Rubiaceae: *Psychotria umbellate* Thonn.	[27]
1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid	Asteraceae: *Cichorium endivia* L.	[60]
Tetrahydroharmine	Malpighiaceae: *Banisteriopsis caapi* (Spruce ex Griseb.) Morton; Zygophyllaceae: *Peganum harmala* L.	[36, 59]
Vallesiachotamine	Rubiaceae: *Chimarrhis turbinata* DC., *Palicourea rigida* Kunth, *Psychotria bahiensis* DC., *P. suterella* Müll. Arg., *P. laciniata* Vell.	[27]
Yohimbine	Apocynaceae: *Aspidosperma discolor*A. DC., *A. excelsum* Benth, *A. eburneum* F. Allem, *A. marcgravianum* Woodson, *A. oblongum*A. DC.	[61]

Table 1. Natural sources of some β-carboline and canthinone alkaloids.

3. Alkaloids and biological activity

Many pharmacological properties attributed to β-carboline alkaloids have been described in the literature, which makes it an important class of natural products. Among them, antimalarial, antileishmanial, trypanocidal, antibacterial and antitumor activities are described [38, 44, 62]. The alkaloids described below have studies of LC-HRMS.

A search for antimalarial drugs describes the activity of the alkaloids (+)-8-hydroxymanzamine A and (+)-manzamine A against chloroquine-sensitive D6 and chloroquine-resistant W2 strains of *Plasmodium falciparum*, with half maximal inhibitory concentration (IC_{50}) of 19.5 and 22.0 ng/mL for (+)-8-hydroxymanzamine A, and selectivity index (SI) of 40 and 35, respectively. For (+)-manzamine A, the IC_{50} values are 20.8 and 25.8 ng/mL, with SI of 47 and 38, respectively [44]. Canthin-6-one and 5-methoxycanthin-6-one, isolated from stem bark of *Zanthoxylum chiloperone* var. *angustifolium*, have IC_{50} values on chloroquine/mefloquine-resistant and sensitive strains of *P. falciparum* of 2.0–5.3 and 5.1–10.4 μg/mL, respectively [10].

The β-carboline alkaloids harmane, harmine and harmaline have been reported to possess antileishmanial activity. Harmane, harmine and harmaline have activity against the amastigote forms of *Leishmania infantum*, with IC_{50} values of 0.27, 0.23 and 1.16 μM, respectively. The harmane and harmaline activities against promastigote forms are less pronounced, with IC_{50} values of 19.2 and 116.8 μM, respectively. Harmine inhibits promastigotes with IC_{50} of 3.7 μM [39]. Strictosamide, alkaloid glycoside isolated from the crude ethanol extracts of roots and branches of *Psychotria prunifolia*, has *in vitro* antiprotozoal activity, especially against promastigotes of *Leishmania amazonensis*, with IC_{50} values of 40.7 μg/mL [29]. The alkaloid (+)-8-hydroxymanzamine A has activity against *Leishmania donovani* with $IC_{50}$of 2.5 mg/mL and $IC_{90}$of 6.1 mg/mL, whereas (+)-manzamine A is less active, with IC_{50} of 11.15 mg/mL and IC_{90} of 31.05 mg/mL [44]. Canthin-6-one, isolated from dichloromethane extract of *Z. chiloperone* stem bark, has antileishmanial activity in BALB/c mice infected with *L. amazonensis*. The intralesional treatment with canthin-6-one is able to decrease by 15.0% a lesion weight and the parasite load by 77.6% when compared with the group of untreated mice [12].

Canthin-6-one also has trypanocidal activity. The alkaloid can provoke 90% of anti-amastigote activity and 79% of trypomastigotes lysis in assays using *Trypanosoma cruzi.* The alkaloid

5-methoxy-canthin-6-one, isolated from the leaves of the same species, is able to cause 66.4% of anti-amastigote activity and 75% of trypomastigotes lysis [14]. Harmine also has trypanocidal effect against *Trypanosoma brucei*, with IC_{50} of 74 μM [13].

The β-carboline alkaloids have antiproliferative effects against many tumor cell lines. The mechanism of action is probably associated with DNA intercalation, inhibition of topoisomerase I and II, cyclin-dependent kinase (CDK), and IkB kinase complex [40, 62]. In cytotoxicity assays with (+)-8-hydroxymanzamine A and (+)-manzamine A, the IC_{50} are, respectively, 0.47 and 1.0 μg/mL against SK-MEL (human malignant melanoma); 0.78 and 1.0 KB μg/mL against KB (human epidermoid carcinoma); 0.75 and 1.1 μg/mL against BT-549 (human breast ductal carcinoma); 0.51 and 4.40 μg/mL against $HepG_2$ (human hepatocellular carcinoma); and 1.25 and 2.15 μg/mL against LLC-PK_{11}(pig kidney epithelial cells) [44]. Canthin-6-one has in vitro cytotoxicity against many cell lines, such as CHO (IC_{50} = 7.529 μM/mL), HepG2 (IC_{50} = 4.551 μM/mL), HeLa (IC_{50} = 14.9 μM/mL), the human epidermoid carcinoma cell line A-431 (IC_{50} = 8.393 μM/mL), the human breast cancer cell line MCF-7 (IC_{50} = 5.541 μM/mL) [9] and MRC5 (fibroblasts) (IC_{50} = 12.1 μg/mL) [10]. The alkaloid 9-methoxy-canthin-6-one has high in vitro cytotoxicity in MCF-7 and A-549 cells (adenocarcinomic human alveolar basal epithelial cells), with IC_{50} of 4.5 and <2.5 μg/mL, respectively [63].

Antimicrobial activity has also been related to this class of compounds. The alkaloids (+)-8-hydroxymanzamine A and (+)-manzamine A are more potent as antimycobacterial than the control ciprofloxacin, with IC_{50} values of 0.13 and 0.36 μg/mL against *Mycobacterium intracellulare* vs. 0.48 μg/mL of ciprofloxacin. However, both substances were inactive against the filamentous fungus *Aspergillus fumigatus* and the Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* [44].

Canthin-6-one, 9-hydroxycanthin-6-one and 10-hydroxycanthin-6-one show active in the anti-inflammatory assays involving LPS-induced nitric oxide (NO), a proinflammatory mediator, in RAW 264.7 cells (murine macrophage from blood) with IC_{50} values ranging from 7.73 to 15.09 μM [64].

4. Ionization source and mass analyzers

An analysis of a sample comprises ionization where the ion beam is accelerated by an electric field and then a mass analyzer, a region of the mass spectrometer where the ions are separated according to their mass/charge ratio (m/z) [65].

There are many different ionization methods, such as ESI, APCI, FAB, suitable for different applications. Many types of mass analyzers are used according to the type and objectives of the analysis: e.g., dual focus, quadrupole, ion trap, time-of-flight (TOF), Orbitrap and Fourier transform ion cyclotron resonance (FT-ICR) mass analyzers are the magnetic sectors [66]. According to this review, the most used mass analyzers for the analysis of β-carbonyl and canthinone alkaloids are the quadrupole, ion trap, TOF and Orbitrap. The most articles reported TOF as the most used analyzer followed by Orbitrap. TOF is based on the simple idea that the speed of two ions created at the same instant with the same kinetic energy will vary according to the mass of the ion (the lighter ion will be faster), when traveling against

the mass spectrometer detector. The main characteristics are as follows: simultaneous analysis of all produced ions, high sensitivity and high mass resolution, which requires very fast data acquisition and detection systems. An Orbitrap mass analyzer is an ion trap comprising a barrel type electrode and an inner coaxial electrode similar to a reel holding the ions in an orbital motion inside the trap [66].

Table 2 presents some LC-HRMS data analysis used to identify β-carboline and canthinone alkaloids. These alkaloids are listed in **Table 1** and have publications demonstrating analyses by LC-HRMS.

Name	Ionization source and mode	Mass analyzer	Found mass $[M+H]^+$	Refs.
Brunnein A	ESI+	FT-ICR	245.0919	[54]
Canthin-6-one	ESI+	Triple QTOF	221.0707	[24]
Canthin-6-one-3N-oxide	ESI+	Triple QTOF	237.0658	[24]
β-Carboline-1-propionic acid	ESI+	Triple QTOF	241.0973	[24]
5,9-Dimethoxycanthin-6-one	ESI+	Triple QTOF	281.0913	[24]
9,10-Dimethoxycanthin-6-one	ESI+	Triple QTOF	281.0913	[24]
11-O-β-D-Glucopyranosylcanthin-6-one	ESI+	Triple QTOF	399.1202	[24]
1-(2-Guanidinoethyl)-1,2,3,4-tetrahydro-3-(hydroxymethyl)-β-carboline	ESI+	Triple QTOF	288.1824	[23]
Harmane	ESI+	FT-ICR	183.09152	[54]
11-Hydroxy-10-methoxycanthin-6-one	ESI+	Triple QTOF	267.0752	[24]
1-Hydroxy-11-methoxycanthin-6-one	ESI+	Triple QTOF	267.0752	[24]
5-Hydroxy-4-methoxycanthin-6-one	ESI+	QTOF	267.0758	[43]
10-Hydroxy-9-methoxycanthin-6-one	ESI+	Triple QTOF	267.0752	[24]
10-Hydroxy-antirhine	ESI+	Synapt HDMS	313.1920	[29]
10-Hydroxyantirhine N-oxide derivative	ESI-	Synapt HDMS	327.1712	[29]
11-Hydroxycanthin-6-one	ESI+	Triple QTOF	237.0658	[24]
(*R*)-5-(1-Hydroxyethyl)-canthine-6-one	DART-SVP+	AccuTOF-TLC	265.1006	[18]
10-Hydroxy-iso-deppeaninol	ESI+	Synapt HDMS	327.1693	[29]
(+)-8-Hydroxymanzamine A	ESI+	FT	565.3608	[44]
(+)-8-Hydroxymanzamine A hydrochloride	ESI+	FT	565.3560	[44]

Name	Ionization source and mode	Mass analyzer	Found mass $[M+H]^+$	Refs.
6-Hydroxymetatacarboline A	ESI+	Orbitrap	398.1348	[4]
6-Hydroxymetatacarboline B	ESI+	Orbitrap	526.1934	[4]
6-Hydroxymetatacarboline C	ESI+	Orbitrap	485.1668	[4]
6-Hydroxymetatacarboline D	ESI/MALDI+	Orbitrap	499.1828	[4]
6-Hydroxymetatacarboline E	ESI+	Orbitrap	469.1721	[4]
6-Hydroxymetatacarboline F	ESI+	Orbitrap	497.2032	[4]
6-Hydroxymetatacarboline G	ESI+	Orbitrap	511.2192	[4]
6-Hydroxymetatacarboline H	ESI+	Orbitrap	545.2031	[4]
6-Hydroxymetatacarboline I	ESI+	Orbitrap	511.2192	[4]
7-Hydroxy-β-carboline-1-propionic acid	ESI+	Triple QTOF	257.0915	[24]
Isovallesiachotamine	ESI+	TOF	351.1696	[27]
Lyaloside	ESI+	TOF	527.1982	[27]
(+)-8-Manzamine A	ESI+	FT	549.3592	[44]
(+)-Manzamine A hydrochloride	ESI+	FT	549.3550	[44]
Metatacarboline A	ESI+	Orbitrap	382.1398	[4]
Metatacarboline B	ESI+	Orbitrap	510.1987	[4]
Metatacarboline C	ESI+	Orbitrap	469.1721	[4]
Metatacarboline D	ESI+	Orbitrap	483.1879	[4]
Metatacarboline E	ESI+	Orbitrap	453.1770	[4]
Metatacarboline F	ESI+	Orbitrap	481.2084	[4]
Metatacarboline G	ESI+	Orbitrap	495.2241	[4]
9-Methoxy-3-methylcanthin-5,6-dione	ESI+	Triple QTOF	281.0913	[24]
9-Methoxycanthin-6-one	ESI+	Triple QTOF	251.0817	[24]
9-Methoxycanthin-6-one-3N-oxide	ESI+	Triple QTOF	269.0811	[24]
1-Methoxymethyl-β-carboline	ESI+	Triple QTOF	213.0990	[24]
Norharmane	ESI+	FT-ICR	169.0760	[54]
Speciogynine	ESI+	Orbitrap	399.22766	[53]
Strictosamide	ESI+	TOF	499.2083	[27]
1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid	ESI+	QTOF	217.0963	[67]
Vallesiachotamine	ESI+	TOF	351.1696	[27]
Yohimbine	ESI+	Quadrupole-Orbitrap	355.2016	[68]

Table 2. LC-HRMS data of β-carboline and canthinone alkaloids.

5. Mass fragmentograms

The observed masses of the fragments in LC-HRMS of the main cited β-carboline and canthinone alkaloids are shown below (**Figure 1**). The principal peaks are shown in the fragmentograms below. The fragments are based on characteristic alkaloid breaks and/or proposals based on mass spectrometry theory.

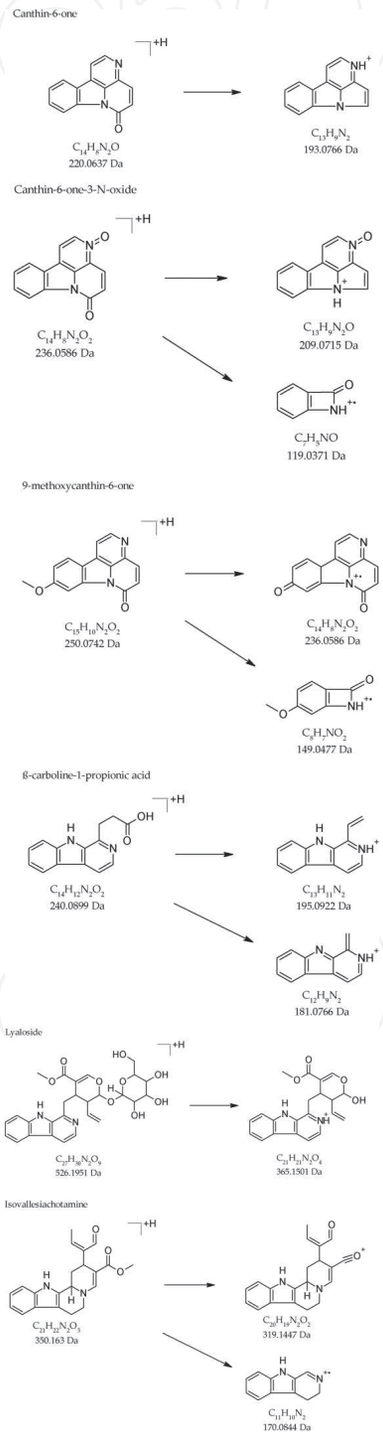

Figure 1. Fragmentogram of β-carboline and canthinone alkaloids.

http://dx.doi.org/10.5772/68075

6. Advantages and disadvantages of the LC-HRMS as analytical tool

The natural product research requires the development of fast and robust techniques for the difficult identification of substances in samples of plant extracts. Actually, GC-MS and LC-MS/MS are more used techniques than LC-HRMS for the identification of plant metabolites. However, the advantages of LC-HRMS and the chemical complexity of plant extracts can justify the investment in that newer technique.

Compared with gas chromatography (GC), techniques involving liquid chromatography (LC) have the advantage of being applicable to a wider variety of chemical classes of compounds. In GC, the analytes must be in gaseous form, and some substances must be hydrolyzed or derivatized to lower polarity and increase volatility to be analyzed. In LC, the analytes must be soluble in the liquid mobile phase and works well with polar substances. LC-MS/MS also has higher sensitivity than GC-MS [65, 69].

GC-MS has a single quadrupole mass detector, whereas LC-MS/MS has two quadrupole detectors in tandem. In MS/MS, only one ion from the first detector, frequently the molecular ion is fragmented in the second detector. The selected-ion monitoring (SIM) mode can be applied for GC-MS to increase sensibility and consists of the selection of three of the more abundant ions from the mass spectrum to be measured by the spectrometer and the comparison between the abundance relative ratio of these ions with the predetermined ratio for the suspect substance. The presence of contaminants affects the ion ratio hinders the identification. The selected reaction monitoring (SRM) mode is applied for LC-MS/MS and consists of the selection of some ions fragmented in the second detector. Thus, LC-MS/MS has more specificity than GC-MS, because two substances with the same nominal mass will exhibit different fragmentations in the second detector. Therefore, SIM or SRM is suitable only for targeted substances. GC-MS and LC-MS/MS can also be employed for the analyses of unknown compounds, but only in the full-scan MS mode and with lower sensitivity. Both GC-MS and LC-MS/MS have resolution of 1 atomic mass unit (amu) [65].

The LC-HRMS has the characteristics of the accurate mass measurement of the analytes, which confers many advantages as compared to other techniques of analysis traditionally used. The mass resolution is about 2 ppm, which represents an error of 0.0006 amu for substances of 300 amu [65]. The exact molecular ion mass is associated with an exact molecular formula of the analyte, a valuable structural information. The exact mass is a calculated parameter, while other techniques depend on experimental results for comparison. Therefore, the main advantage of LC-HRMS is that it allows the identification of a wider number of analytes, including unexpected substances in the sample, and does not require reference standards or preexisting MS libraries for comparison [70]. Additionally, LC-TOF/MS can be applied to a larger range of molecular masses (up about 20,000 amu), while LC-MS/MS is indicated for substances up to about 3000 amu [65].

Besides the high mass resolution, the LC-HR/MS has other important advantages. A previous chromatographic treatment of the sample is not required, and a robust method for qualitative analysis can be applied for different and unknown samples, even for the identification of minority substances. Thus, analyses are faster than in LC-MS/MS, because the time in the development of the method is saved. It is especially interesting in natural product studies

which frequently are related to complex mixtures, as in metabolomics, extract authentication and screening studies [70–74].

However, given the high complexity of many substances of plant origin, it is important to carry out analyzes using different ionization modes and both polarities. Most alkaloids are detectable in positive mode, either for ESI or APCI, but the matrix interference is more pronounced. The formation of adducts is possible, more specifically, cationization in positive mode may lead to the formation of alkali adducts, with the formation of multimers that add ions to the mass spectrum [73].

The LC-QTOF/MS adds the high mass resolution to mass fragmentation, which provides higher confidence in identification, although with higher cost. Comparing LC-QTOF/MS to LC triple quadrupole linear ion trap (QqLiT), the first leads to fewer false positives, but the latter has slightly lower detection limits in most situations [74].

Besides the high cost, LC-HRMS has the disadvantage of not differentiating structural isomers, which is important in phytochemistry since substances with more than one stereocenter are common. In those cases, it is necessary to complement with other information, such as retention time and spectroscopic data [73]. Another disadvantage is the rapid saturation of the detector, which requires work with more diluted samples [65]. It is expected that these equipments will become less costly, so that the technique will gain wide use.

7. Analysis of alkaloids in body samples by LC-HRMS

Plant species that contain β-carboline alkaloids, including canthinone alkaloids, are widely employed therapeutically or even as a drug of abuse. Given the diversity of the biological activities already described for these alkaloids, including neurological effects, it is necessary to develop techniques for the detection and quantification of these alkaloids and their metabolites in biological fluids and tissues, as a tool for toxicological analysis and pharmacokinetic studies. This knowledge may also be the starting point for the development of new drugs with potential commercialization.

LC-HRMS is promising in toxicological and analytical studies of metabolism, where substances are often unexpected, and the sample is available in small amount. In addition, it provides rapid analysis and the possibility of using a general method for a wide variety of substances [65, 74–76]. To date, there are few studies using LC-HRMS for the analysis of alkaloids, including β-carboline alkaloids in biological samples, possibly because of the still very high equipment prices. Frequently, LC-MS/MS or GC/MS is used previously, and only after the high-resolution mass is obtained for confirmation.

Biological samples, such as blood, bile, urine, milk, feces and pineal dialysates, consist of a complex matrix, which may cause interference in LC-MS analyses of low or high resolution. Therefore, it is common to submit samples to a pretreatment by solid phase extraction (SPE), using HCX cartridge [53, 76] or C18 cartridges [43, 53, 68]. However, in some cases,

the sample is simply extracted with an organic solvent, such as the procedure described by Shi et al. [32] for the analysis of 5-hydroxy-4-methoxycanthin-6-one and its metabolites, that uses ethyl acetate to extract the analytes from plasma and methanol for feces collected from male Sprague-Dawley rats. There are cases that no pretreatment is required, such as in the analysis of β-carbolines (1,2,3,4-tetrahydro-β-carboline, 2-methyl-1,2,3,4-tetrahydro-β-carboline, 6-hydroxy-tetrahydro-β-carboline, and 6-methoxy-tetrahydro-β-carboline), metabolites of dimethyltryptamine and derivatives, in pineal gland microdialysate collected from male Wistar rats [68].

A large variety of phase I metabolites of β-carboline alkaloids, formed by N-decarbonylation, oxidation and methylation, and phase II metabolites, formed by conjugation, such as glucuronides, sulfates and N-acetylcysteine derivatives, are present in body samples. For analysis of phase I metabolites, β-glucuronidase and/or arylsulfatase enzymes can be added to the sample for cleavage of conjugates and to avoid interferences of phase II metabolites [43, 53, 68, 76].

The liquid chromatography step is similar for low and high mass resolution. The separation can occur in TF Hypersil Gold C18 column, 100 mm × 2.1 mm, 1.9 μm [53]; Hedera ODS-2 C18 column, 250 mm × 4.6 mm, 5 μm [43]; C18 BEH column, 100 mm × 2.1 mm, 1.7 μm [67]; Zorbax Eclipse Plus C18, 100 mm × 3.0 mm, 3.5 μm [68]; Superspher 60 RP-8 column, 125 mm × 2 mm, 5 μm [76]; Zorbax Eclipse Plus rapid resolution HT C18 column, 50 mm × 2.1 mm, 1.8 μm [75]. The oven temperature is set at 30°C [43], 35°C [53] or 40°C [75]. After pretreatment, samples are frequently diluted in methanol or in mobile phase before injection in LC systems. The mobile phase is frequently a gradient from formic acid (0.05 or 0.1%) in water to acetonitrile, with or without formic acid [43, 68, 76]. This aqueous phase may be replaced by an aqueous solution containing ammonium formate buffer (2.5 or 10 mM) with 0.1% (v/v) formic acid [53, 75]. The organic phase may be 0.1% formic acid in acetone:acetonitrile 20:80 [67]. The solution B of the method developed by Kolmonen et al. [75] consists of 2.5 mM ammonium formate and 0.1% formic acid in 90% acetonitrile. The flow rate varies from 300 μL/min [68] to 1 mL/min [43]. The total run time varies from 8 min [75] to 67 min [53].

In general, the MS analyzer, TOF or Orbitrap, employs electrospray ion source. For this class of substances, the positive ionization mode is the most applied (ESI+) [43, 53, 67], although it is more appropriate to use both positive and negative ionization modes in screening analyses to cover more substances [68, 75]. Capillary voltage varied from 3 to 4.5 kV, [43, 53, 67, 68, 75] and resolution varies from 7500 to 60,000 [46, 53]. After the analysis, data processing is necessary with suitable software to help in the identification of metabolites.

Although LC-HRMS has been more used to confirm identification, the technique can be used alone successfully in screening, as the methodology proposed by Kolmonen et al. [75]. The methodology uses LCTOFMS for the search of doping agents in human urine. The method is applicable to at least 207 analytes, including the indole alkaloid strychnine, and may even be used for quantitative analyzes for many of this substances. After an SPE sample pretreatment, the analysis run time is 8 min for each ionization mode, with a total time of 16 min.

Some β-carboline alkaloids and their metabolites have been identified in biological tissues and fluids, such as tetrahydro-β-carboline derivatives—present in plant species and also considered

an endogenous alkaloid; [43, 67, 68] speciogynine—isolated from *Mitragyna speciosa*, a plant species used as drug of abuse [53]; 1-methyl-3-carboxy-β-carboline—found in cow milk probably derived from the diet and metabolism [76]. The technique is still expanding, and the few works found in the literature indicate a great potential not yet explored.

8. Summary

An important class of natural products found in Angiosperms, β-carboline and canthinone alkaloids, has various pharmacological properties and toxic effects. Coupled chromatographic and mass spectrometric techniques can be used to identification of these alkaloids. In this chapter, an approach overview of LC-HRMS applied to chemical complexity of plant extracts and forensic samples containing β-carboline and canthinone alkaloids can be a good choice technique to analyze and elucidate this kind of compounds. In addition, the HRMS/MS fragments of some important β-carboline and canthinone alkaloid are shown in mass fragmentograms schemes. Among important advantages of LC-HRMS, the main one is that it allows the identification of a wider number of analytes, including unexpected substances in the sample, and does not require reference standards or preexisting MS libraries for comparison. This technique can be used alone successfully in screening since it provides rapid analysis and the possibility of using a general method for wide variety of substances.

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