Supplemental Material

Polyamine-containing natural products: structure, bioactivity, and biosynthesis

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Content

Tab. S1 The sources and bioactivities of polyamine-containing natural products

Compounds	No.	Organisms	Bioactivities	Ref.
Plants				
Scotanamines A-D	**14-17**	*Scopolia tangutica*	μ-opioid receptor agonist	[1]
Trihydroxycinnamoyl spermidines	**18-22**	Eudicotyledons (Rosaceae, Asteraceae, Liliaceae, Solanaceae, Fabaceae, Pandaceae, etc.)	Antibacterial (G^+), antifungal, antiviral, anti-depression, and antioxidative	[2-6]
Dovyalicins A-F and H-I	**29-36**	Salicaceae (*Dovyalis macrocalyx*, *D. abyssinica*, *D. hebecarpa*, *Homalium cochinchinensis*)	Cytotoxicity	[7-9]
Lycibarbarspermidines A-O, and T	**82-97**	*Lycium barbarum*	Anti-AD (Alzheimer' s disease), antioxidative, anti-inflammatory	[10, 11]
Lyciamarspermidines A-C	**98-100**	*Lycium* sp.	Anti-inflammatory	[12]
Lyciamarspermines A and B	**101, 102**	*Lycium* sp.	-	[12]
Capparispine, capparispine 26-O-β-D-glucoside	**103, 104**	*Capparis spinosa*	-	[13]
Cadabacine	**105**	*Cadaba farinose*	Antiparasitic	[14, 15]
Cadabacine 26-O-β-D-glucoside	**106**	*Capparis spinosa*	-	[13]
Dracotanosides A-D	**107-110**	*Dracocephalum tanguticum*	-	[16]
Hyssopusizine	**111**	*Hyssopus cuspidatus*	Antifungal	[17]
Meehanines A-W	**112-134**	*Meehania urticifolia*	-	[18, 19]
(±)-Orychoviolines A and B	**135-138**	*Orychophragmus violaceus*	Radioprotective activity	[20]
Lunarine, lunaridine	**139, 140**	*Lunaria biennis, L. rediviva, L. annua*	Antitrypanosomal	[21]
Androderine, (+)-decaryine A, (-)-decaryine B	**141-143**	*Androya decaryi*	-	[22]
Meefarnines A and B	**144, 145**	*Meehania fargesii*, *Dendrobium officinale*	Hyaluronidase inhibitory activity	[23]

Celacarfurine	**146**	*Tripterygium wilfordii*	Anti-inflammation	[24]
Gymnarine	**147**	*Gymnosporia arenicola*	-	[25]
Bacteria				
Phevamine A	**26**	*Pseudomonas syringae*	Suppress plant immune responses	[26]
JBIR-94, JBIR-125	**27, 28**	*Streptomyces* sp.	Antioxidative, antibacterial (G^-), anticancer	[27]
Propanochelin, butanochelin, pentanochelin	**148-150**	*Acinetobacter bouvetii*	Iron-chelating	[28]
Lysochelin	**151**	*Lysobacter enzymogenes*	Iron-chelating	[29]
Serratiochelins A-C	**152-154**	*Serratia marcescens*	Iron-chelating, antitumor, antibacterial (G^+)	[30, 31]
Petrobactin	**156**	*Marinobacter hydrocarbonoclasticus*, *Bacillus anthracis*, *B. cereus*, *Alteromonas macleodii*	Iron-chelating	[32-34]
Fimsbactins A-D and F	**157-161**	*Acinetobacter baumannii*, *Acinetobacter baylyi*	Iron-chelating	[35]
Photobactin	**162**	*Photorhabdus luminescens*	Iron-chelating, antibiosis	[36]
Vibriobactin	**163**	*Vibrio cholerae*	Iron-chelating	[37]
Vulnibactin and related molecule	**164, 165**	*Vibrio vulnificus*	Iron-chelating	[38]
Fluvibactin	**166**	*Vibrio fluvialis*	Iron-chelating	[39]
Nigribactin	**167**	*Vibrio nigripulchritudo*	Iron-chelating	[40]
Agrobactin	**168**	*Agrobacterium tumefaciens*, *Paracoccus denitrificans*	Iron-chelating	[41, 42]
Parabactin	**169**	*Paracoccus denitrificans*	Iron-chelating	[42]
Labrenzbactin	**170**	*Labrenzia* sp.	Iron-chelating	[43]
Putrebactin	**171**	*Shewanella putrefaciens*	Iron-chelating	[44]
Avaroferrin	**172**	*Shewanella algae*	Iron-chelating	[45]
Bisucaberin	**173**	*Alteromonas haloplanktis*, *Vibrio salmonicida*	Iron-chelating	[46, 47]
Aculeolamides A and B	**174, 175**	*Streptomyces aculeolatus*	Iron-chelating, antitubercular, antimalarial	[48]
Desferrioxamines B, E	**176-178**	*Streptomyces coelicolor,*	Iron-chelating	[49, 50]

and G_1		*Erwinia amylovora*		
Fulvivirgamides A_2, B_2, B_3, and B_4	**179-182**	*Fulvivirga* sp.	Iron-chelating	[51]
Acinetoferrin	**183**	*Acinetobacter haemolyticus*	Iron-chelating	[52]
Rhizobactin 1021	**184**	*Rhizobium meliloti* 1021, *Sinorhizobium meliloti*	Iron-chelating	[53, 54]
Synechobactins A-C	**185-187**	*Synechococcus* sp.	Iron-chelating	[55]
Schizokinen	**188**	*Bacillus megaterium*, *Rhizobium leguminosarum*	Iron-chelating	[56, 57]
Fradiamines A and B	**189, 190**	*Streptomyces fradiae*	Iron-chelating, antibacterial	[58]
Malleobactins A-H	**191-198**	*Burkholderia mallei*, *B. pseudomallei*	Iron-chelating	[59, 60]
Crochelins A-D	**199-202**	*Azotobacter chroococcum*	Iron-chelating	[61]
Ornibactins C_4, C_6, and C_8	**203-205**	*Pseudomonas cepacia*, *Burkholderia cenocepacia*	Iron-chelating	[62, 63]
Ferrisiderophore	**206**	*Burkholderia xenovorans*	Iron-chelating	[64]
Caribactins A-F	**207-212**	*Paraburkholderia caribensis*	Iron-chelating	[65]
Glidonins A-L	**213-224**	*Schlegelella brevitalea*	Cytotoxicity, antitumor	[66]
Edeines A, B, D, and F	**225-228**	*Brevibacillus brevis*	Antibacterial (both G^+ and G^-), antifungal, antitumor, immunosuppressive activities	[67, 68]
Paenilamicins A1, A2, B1, and B2	**229-232**	*Paenibacillus larvae*	Antibacterial (G^+), antifungal	[69]
Galantin I	**233**	*Paenibacillus pulvifaciens*	Antibacterial (both G^+ and G^-)	[70]
Pingyangmycin	**234**	*Streptomyces pingyangensis*	Anticancer	[71]
Boanmycin	**235**	*Streptomyces pingyangensis*	Anticancer	[72]
Boningmycin	**236**	*Streptomyces verticillus var. pingyangensis n.sp.*	Anticancer	[73]
Zeamine, zeamine I, and zeamine II	**247, 248, 10**	*Dickeya zeae*, *Serratia plymuthica*	Antibacterial (both G^+ and G^-), antifungal, nematicidal	[74-76]
Fabclavines Ia, Ib, IIa, IIb, IIIc, IIId, IVa, and IVb	**249-256**	*Xenorhabdus szentirmaii*, *X. budapestensis*	Antibacterial (both G^+ and G^-), antifungal, antiprotozoan and nematicidal	[77, 78]

Truncated fabclavine derivatives	**257-260**	*Xenorhabdus szentirmaii*	Antibacterial (both G^+ and G^-), antifungal	[79]
Fungi				
Flavunoidine	**60**	*Aspergillus flavus*	-	[80]
Pistillarin	**155**	Basidiomycetes (*Clavariadelphus pistillaris*, *Ramaria* sp., *Gomphus floccosus*), *Penicillium bilaii*	Iron-chelating, antioxidative	[81-83]
Marine sponges				
Normonachocidins A, B, D, G, and H	**37-41**	*Monanchora pulchra*	Anticancer	[84, 85]
Monanchomycalins A-C	**42-44**	*Monanchora pulchra*	Anticancer	[86, 87]
Ptilomycalin A	**45**	*Ptilocaulis spiculifef*, *Monanchora pulchra*	Anticancer	[87, 88]
Monanchoxymycalins A and B	**46, 47**	*Monanchora pulchra*	Anticancer	[89]
Halitulin	**48**	*Haliclona tulearensis*	Antitumor	[90]
Isohalitulin	**49**	*Haliclona tulearensis*	Toxicity	[91]
Haliclorensin	**50**	*Haliclona tulearensis*	-	[92]
Haliclorensin B	**52**	*Haliclona tulearensis*	Toxicity	[91]
Haliclorensin D	**53**	*Neopetrosia chaliniformis*	-	[93]
Neopetrocyclamines A and B	**54, 55**	*Neopetrosia* cf *exigua*	-	[94]
Papuamine, haliclonadiamines	**56, 57-59**	*Haliclona* sp., *Halichondria panicea*, *Neopetrosia* cf *exigua*	Antibacterial (G^+), antifungal, anticancer	[94-98]
Ianthelliformisamines A-C	**61-63**	*Suberea ianthelliformis*	Antibacterial (both G^- and G^+)	[99]
Tokaradine C	**64**	*Pseudoceratina purpurea*	Insecticidal	[100]
Spermatinamine	**65**	*Pseudoceratina* sp.	Antibacterial (G^-), isoprenylcysteine carboxyl methyltransferase (Icmt) inhibitor	[101]
Pseudoceramines A-D	**66-69**	*Pseudoceratina* sp.	Antibacterial (G^-)	[102]
Pseudoceratidine	**70**	*Pseudoceratina purpurea*	Antifouling, antibacterial (both G^+ and G^-), antifungal	[103, 104]
Pseudoceratidine derivatives	**71-75**	*Tedania brasiliensis*	Antiparasitic	[105]

Tedamides A-D	**76-79**	*Tedania brasiliensis*	Antiparasitic	[105]
Aculeine B	**245**	*Axinyssa aculeate*	Cytotoxicity, neuroactive	[106]
Protoaculeine B	**246**	*Axinyssa aculeate*	-	[107, 108]
Insects				
Philanthotoxin-433	**23**	*Philanthus triangulum*	Non-competitive glutamate receptor inhibitor, toxin, visual function protection	[109, 110]
PA366	**24**	Theraphosidae (*Acanthoscurria geniculate*, *Chilobrachys penang*, *Phlogius* sp., *Psalmopoeus irminia*)	Anticancer, cytotoxicity	[111]
PA389	**25**	Theraphosidae (*Ceratogyrus darlingi*, *Harpactirella sp.*), Hexathelidae (*Atrax robustus*), Ctenizidae (*Hebestatis theveneti*)	Cytotoxicity	[111]
Sea squirt				
Didemnidines A and B	**80, 81**	*Didemnum* sp.	Antiparasitic	[112]
Shark & sea lamprey				
Squalamine	**237**	*Squalus acanthias*, *Petromyzon marinus*	Antibacterial (both G^+ and G^-), antifungal, antiprotozoan, antiviral, antitumor, antiangiogenic, and antiobesity	[113-116]
PASs 1-7	**238-244**	*Squalus acanthias*	Antibacterial (both G^+ and G^-), antifungal, antiprotozoan, antiviral, antitumor, antiangiogenic, and antiobesity	[116, 117]

Notes:

1. The colors in the text represent different classes of polyamine-containing natural products.

Green: polyamine alkaloids;

Blue: polyamine siderophores;

Orange: NRP-(PK)-PA hybrids;

Blue grey: polyaminosterols;

Lavender: peptide-lcPA;

Red: NRP-PK-lcPFAN hybrids.

2. A dashed line “-” indicates that the compound is inactive or the activity of the compound has not been evaluated.

Tab. S2 Proteins predicted to be involved in the attachment of the polyamine moiety to the scaffolds

Protein	Proposed function	Products	No.	Ref.
GspSA	ATP-grasp enzyme, ATP-dependent condensation glutathione and Spd	Glutathionylspermidine	[a]	118
HsvC	Putative ATP-grasp enzyme, ATP-dependent condensation L-Val and guanyl-Spd	Prephevamine A	**276**	26
AsbA	Type A NIS synthetase, ATP-dependent condensation citric acid and Spd	Petrobactin	**156**	119
AsbB	Type C NIS synthetase, ATP-dependent condensation N^8-citryl-Spd or N^1-(3,4-DHB)-N^8-citryl-Spd and Spd			120
FbsG	NRPS (C-T-C), condensation T-bound thioester intermediate and N^1-acetyl-N^1-hydroxy-Put	Fimsbactin A	**157**	35
VibH	NRPS (a stand-alone C domain), condensation ArCP-bound 2,3-DHB and Nspd	DHB-Nspd	**310**	121
BibC[C]	NIS synthetase, ATP-dependent dimerisation and macrocyclisation of HSC	Bisucaberin	**173**	122
DesD	NIS synthetase, ATP-dependent condensation the adenylated HSC homodimer and HAC or trimerization of HSC	Desferrioxamines B, E, and G_1	**176-178**	123
FulD	NIS synthetase, ATP-dependent trimerization of HSC	Desferrioxamine G_1	**178**	51
Achr_39030	Putative VibH-like protein or A-domain bearing protein, condensation the NRP scaffold and Put	Crochelins B-D	**200-202**	61
GdnB	NRPS module 13 (C_{13}-A*-T-TE), condensation the peptidyl thioester intermediate and Put	Glidonins F-L	**218-224**	66
PamI	BtrH-like protein, condensation the T-bound NRP-PK thioester intermediate and Spd	Prepaenilamicin B2	**336**	69
Zmn19	NRPS (a stand-alone C domain), condensation the ACP-bound NRP-PK thioester intermediate and zeaminne II	Prezeamine I, prezeamine	**352**, **353**	124
FclL	A stand-alone C domain-like protein, condensation the ACP-bound NRP-PK thioester intermediate and lcPFAN-type polyamine **11**	Fabclavine IIa	**251**	79
FlvF	Terpene cyclase-like enzyme, condensation the carbocationic tetracyclic sesquiterpene and dimethylcadaverine	Flavunoidine	**60**	125

Notes:

1. The colors of the text represent different mechanisms involved in the attachment of the polyamine moiety to the scaffolds.

Red: Proposed mechanism (i), ATP-grasp enzyme (**Fig. 30A**);

Blue: Proposed mechanism (ii), acyl-adenylate forming enzyme (**Fig. 30B**);

Green: Proposed mechanism (iii), NRPS with a C or C-like domain (**Fig. 30C**);

Violet: Proposed mechanism (iv), terpene cyclase-like enzyme (**Fig. 30D**).

2. [a] The molecule is not shown in this review.

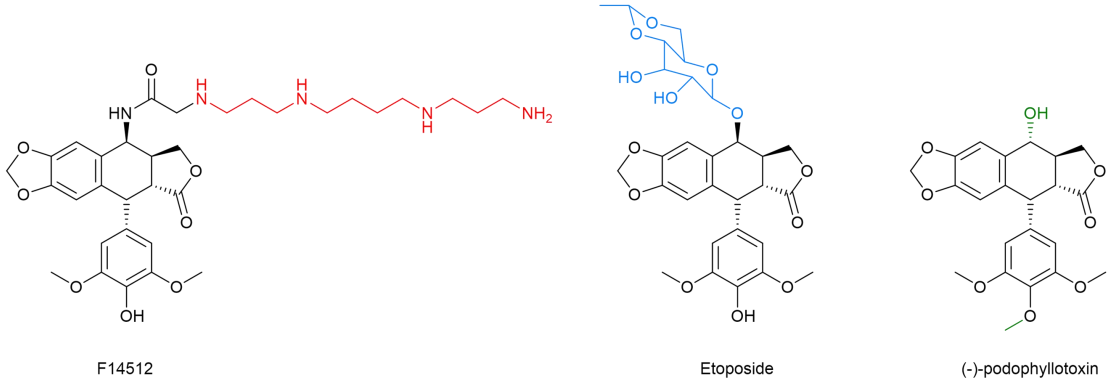

Fig. S1 Structures of two semi-synthetic compounds F14512 and etoposide and their natural precursor (-)-podophyllotoxin

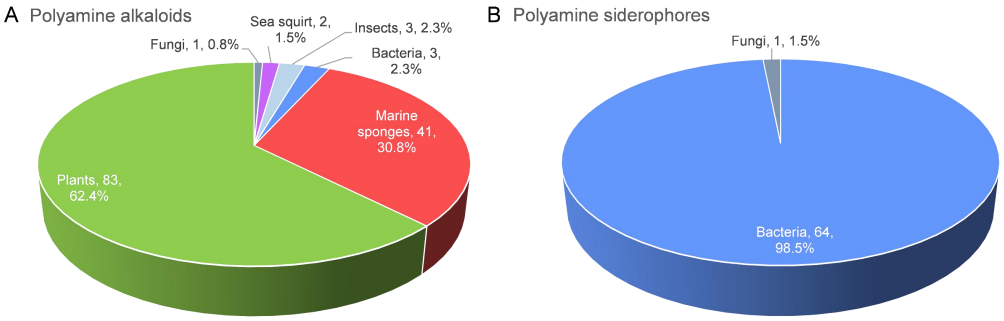

Fig. S2 Source composition of polyamine alkaloids (**A**) and polyamine siderophores (**B**)

In the last 20 years, polyamine alkaloids were discovered mainly from plants (83, 62.4%) and marine sponges (41, 30.8%), but also from other organisms, such as bacteria (3, 2.3%), insects (3, 2.3%), sea squirt (2, 1.5%), and fungi (1, 0.8%).Interestingly, polyamine siderophores were isolated mainly from bacteria (64, 98.5%) and also identified in fungi (1, 1.5%).

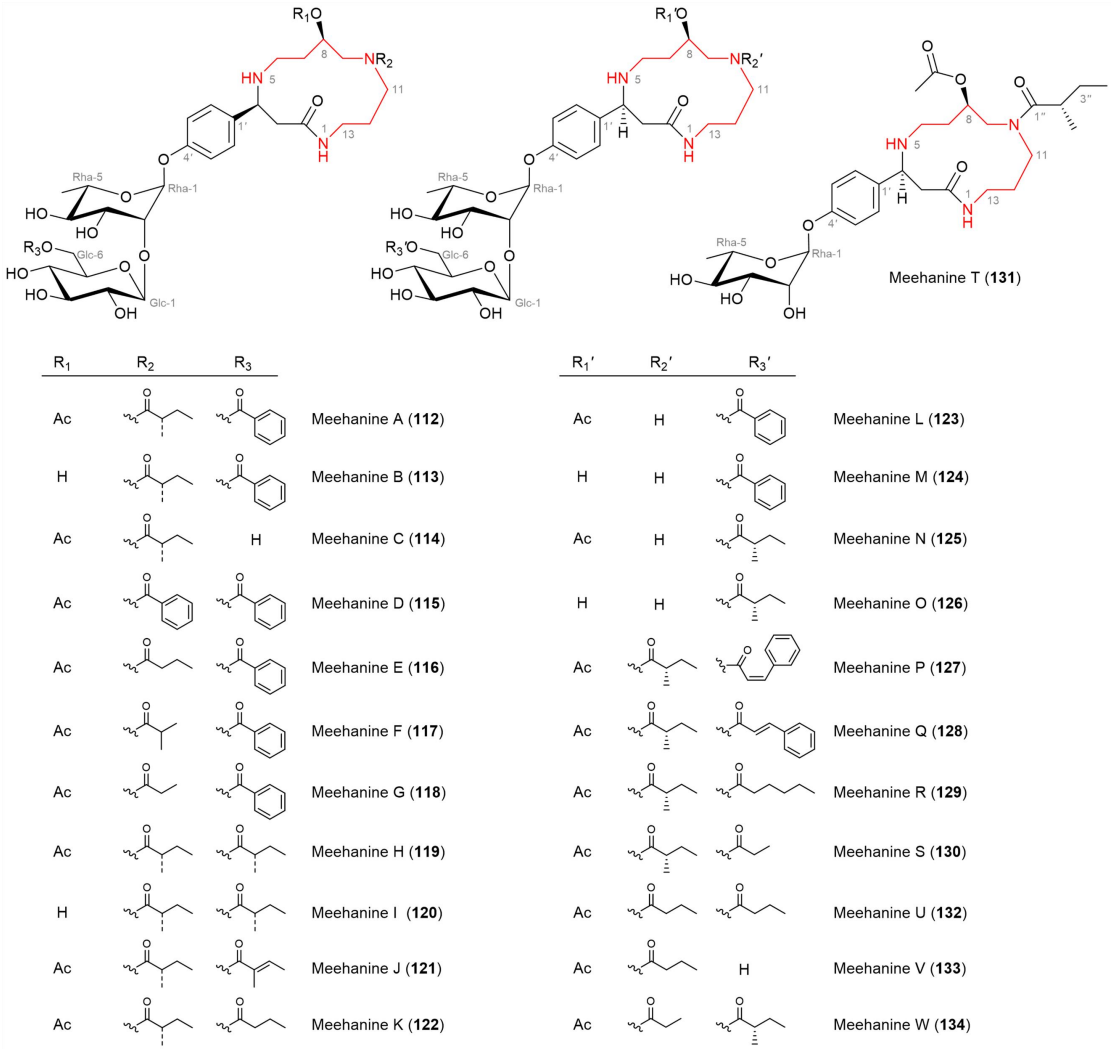

Fig. S3 Structures of meehanines A-W (**112-134**)

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