Natural Product Reports

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal

Cite this: DOI: 10.1039/d5np00090d

A comprehensive review of the structural diversity, biosynthesis and chemical synthesis of *Lasiodiplodia* spp. natural products

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Received 18th December 2025

DOI: 10.1039/d5np00090d

rsc.li/npr

Covering: up to the end of 2025

The genus *Lasiodiplodia* belongs to the Botryosphaeriaceae family. Over the past few decades, it has proven to be a great source of interesting natural products, including depsidones, jasmonates, preussomerins, and β-resorcylic acid derivatives. This review provides an update on the secondary metabolites of 13 species of *Lasiodiplodia* and their bioactivities, covering the period up to the end of 2025. Further insights into their proposed biosynthetic pathways are discussed, and key examples of the synthetic pathways leading to their production are highlighted.

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1 Introduction

Lasiodiplodia is one of the most important plant pathogenic genus of Botryosphaeriaceae, a genus-rich family in the Dothideomycetes class. Species of the genus *Lasiodiplodia* are associated with various host plants, acting as primary or secondary pathogens and even as endophytes that, under stress conditions of the host, can switch their lifestyle and become pathogens.[1,2] Consequently, species under this genus have garnered considerable research attention due to their global distribution and involvement in diseases affecting several economically important plants, causing extensive damage to crops. This is a concern that has further increased with climate change, which is altering the distribution and impact of plant pathogens,[3] including *Lasiodiplodia* spp.[4,5] In fact, rising temperatures have been identified as the main abiotic factor exacerbating the impact of plant diseases by promoting fungal growth and colonization with economically relevant consequences.[5]

Since its introduction in 1894, *Lasiodiplodia* has had an intricate taxonomic history. It was first introduced by Ellis and Everhart with *Lasiodiplodia tubericola* as the type species,[6] although the genus was formally described in 1896 by Clendenin.[7] Subsequently, prevailing over the epithet *tubericola*, *Lasiodiplodia theobromae* (Pat.) Griffon & Maubl. has been

proposed and recognized as the type species of the *Lasiodiplodia* genus. The use of traditional morphology in fungal species identification for many years led to *Lasiodiplodia* being treated as a monotypic genus. This trend ended with the introduction of DNA sequence-based methods, which recognized *L. theobromae* as a complex of different cryptic species[8] and enabled the identification of isolates related to but different from the known taxa.[9,10] Hence, from that moment onwards, the widespread use of biomolecular markers for fungal identification has led to the proliferation of new species belonging to the genus *Lasiodiplodia*, such as *Lasiodiplodia pseudotheobromae*,[8] *Lasiodiplodia mediterranea*,[11] *Lasiodiplodia venezuelensis*[9] and *Lasiodiplodia brasiliensis*.[12] To complicate matters further, until recently, it was common practice in mycology to name both the asexual and sexual stages of the same fungus differently (*i.e.*, dual nomenclature). This nomenclature system increased the confusion within the *Lasiodiplodia* genus because, for example, *Botryosphaeria rhodina* (Berk & M.A. Curtis) Arx was used as the teleomorphic name of *L. theobromae*. This practice is no longer acceptable according to the latest International Code of Nomenclature for algae, fungi, and plants.[13]

Although the employment of new molecular tools for fungal taxonomy has improved the classification, the phylogenetic tree of the genus *Lasiodiplodia* is continuously updated due to the detection of new taxonomic relationships among botryosphaeriaceous fungi that cause reconsiderations of the nomenclature.[14]

Despite the long list of species belonging to the genus *Lasiodiplodia* gradually emerging in recent decades,[15] *L. theobromae* remains the most reported and studied species. This is also due to its great ability to infect a wide range of crops and trees, causing rotting and dieback in most infected plant hosts, thereby resulting in significant yield losses and reduced fruit quality.[16] Furthermore, *L. theobromae* is also recognized as an

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emerging human pathogen associated with several diseases, including onychopathy,[17] keratitis[18] and rhinosinusitis.[19]

Species of *Lasiodiplodia* are prolific sources of secondary metabolites belonging to different classes of natural products and exhibiting a broad range of activities. The diverse secondary metabolism observed in the *Lasiodiplodia* genus may be related to some of the peculiar features of these fungi, such as their global distribution, different symbiotic lifestyles, host adaptability and capacity to cause diverse symptoms in infected hosts. Thus, secondary metabolites produced by *Lasiodiplodia* spp. may be responsible for the dynamic host–fungus–environment interaction, which is critical due to its ecological implications and biotechnological applications.

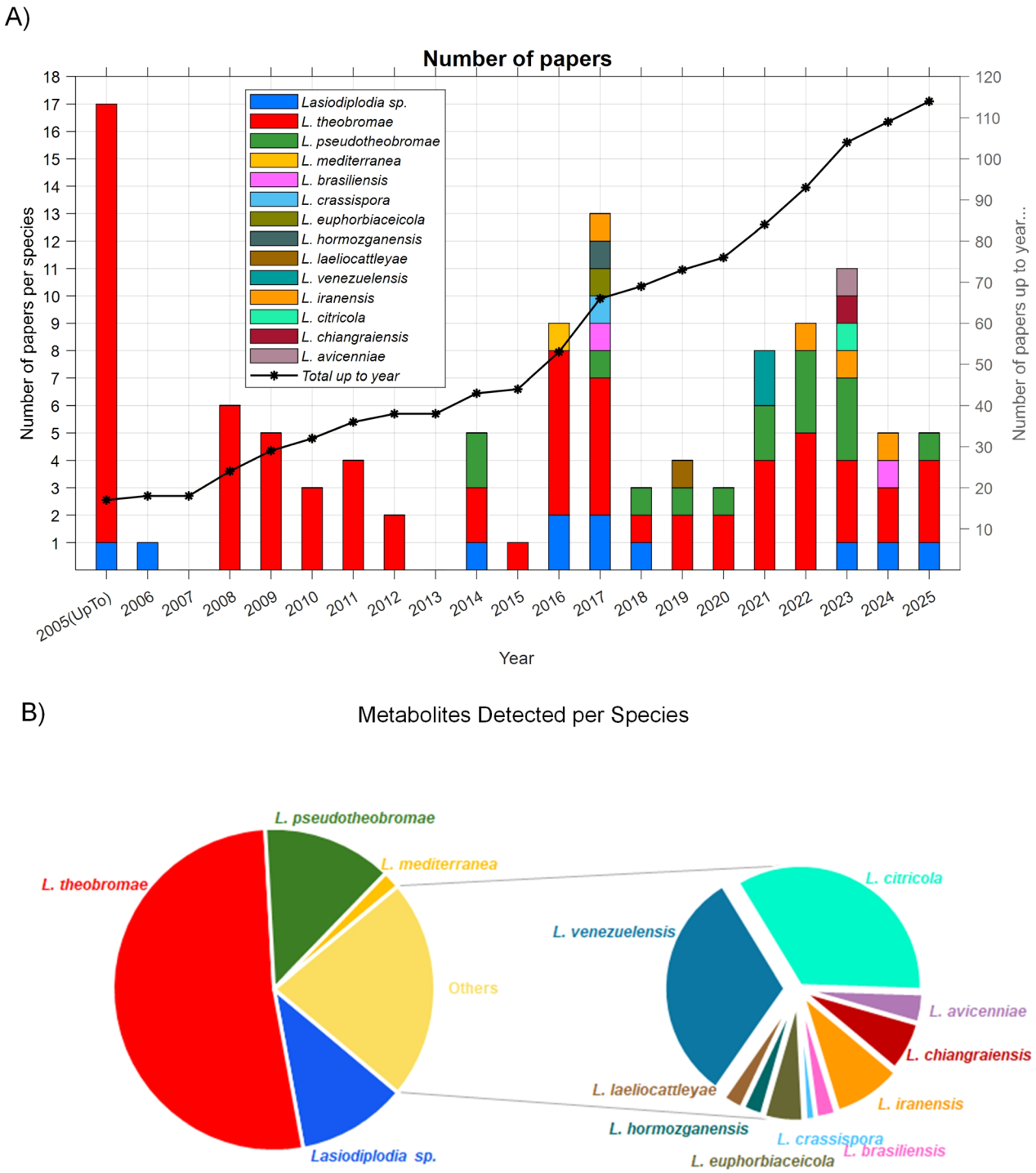

Fig. 1 (A) Evolution of the number of publications on the metabolites of *Lasiodiplodia* spp. over the years. (B) Pie-of-pie chart of the metabolites detected per species.

In this review, we present a comprehensive overview of the secondary metabolites produced by the fungi of the genus *Lasiodiplodia*, their bioactivities, selected biosynthetic pathways and examples of synthetic approaches.

To date, over 270 bioactive compounds have been reported from cultures of the species of *Lasiodiplodia* and many of them showed interesting bioactivities, such as phytotoxic, cytotoxic and antimicrobial activities.

PubMed, Google Scholar, Web of Science, SciFinder and Scopus were used to collect all the published articles about *Lasiodiplodia* spp. natural products. Data are organized in tables and figures according to their chemical structures and then the chemical and biological aspects are discussed.

2 Classification, structures and occurrence of *Lasiodiplodia* spp. natural products

Sixty years ago, Gupta *et al.*[20] described the production, isolation and biological properties of a new secondary metabolite from an isolate of *L. theobromae*, which was named botryodiplodin. Since then, over 270 metabolites have been identified as products of *Lasiodiplodia* spp. and some of them have been reported exclusively from this fungal genus.

The taxonomic and phylogenetic aspects of this fungal genus have long been a research subject, and this has inevitably affected the study of the metabolism of *Lasiodiplodia* spp. (Fig. 1A). In fact, the first decade of the 2000s was crucial for this genus, which, as mentioned in the previous section, experienced dramatic taxonomic changes following the advent of molecular identification to improve fungal characterization and the introduction of the principle "one species-one name" in mycology.[13] Consequently, the study of metabolites produced by species other than *L. theobromae* began about 10 years ago, when the evolution of the publications related to *Lasiodiplodia* metabolites presented a considerable increase in total number (see Fig. 1A). This trend demonstrates a significant and growing interest by the scientific community in the detection of *Lasiodiplodia* metabolites, which is currently related to their structural diversity, bioactivity and implications of their occurrence. Thus far, 13 species belonging to the genus *Lasiodiplodia* have been investigated for the production of secondary metabolites.

The pie charts in Fig. 1B clearly show that, among *Lasiodiplodia* spp., a higher number of metabolites is reported for *L. theobromae*, but we must not forget that this species is also more studied than the other 12 due to its early detection (Fig. 1A). Hence, it is quite possible that the imbalance in metabolite production by *Lasiodiplodia* spp. that emerges from Fig. 1B reflects what has occurred taxonomically for this genus since its first isolation.

Apart from that, *L. theobromae* is a very promising source of bioactive secondary metabolites and, even if less investigated, it seems that all *Lasiodiplodia* spp. share a good ability to produce bioactive compounds *in vitro*.

As can be seen in Fig. 2, compounds produced by fungi from the genus *Lasiodiplodia* can be collected in 15 classes according to their chemical structures. The bubble chart in Fig. 2 allows a quick and compact visualization of the compound abundance in each class, also allowing comparisons by bubble size. It can be easily seen that *Lasiodiplodia* spp. are good producers of compounds that can be classified as "resorcinol and β-resorcylic acid derivatives", "lactones and lactols" and "jasmonates".

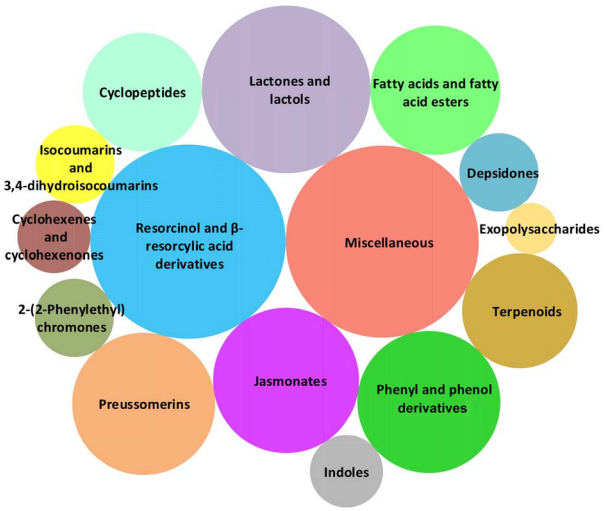

Fig. 2 Bubble chart of the classes of the *Lasiodiplodia* spp. natural products.

For a more organized and clearer discussion, some metabolites have been included in a single class even if they exhibit the proper structural features of two or more classes. This is expected, given the structural complexity of some natural products, which makes a clear separation between the groups impossible.

For completeness, a few primary metabolites occasionally detected in *Lasiodiplodia* spp. cultures are mentioned (*e.g.*, glycerol, succinic acid, and uracil), but they are treated briefly in the following sections to preserve the focus on the structural diversity of secondary metabolites.

It should be noted that manuscripts listing unnatural or frequently occurring compounds as contaminants have been deliberately excluded from the discussion.[21–23]

2.1 Cyclohexenols and cyclohexenones

Cyclohexenols and cyclohexenones are polyhydroxylated polyketides commonly found as natural products.[24–27] Despite their frequent occurrence, to date, these compounds have been identified in the *Lasiodiplodia* genus only from *L. theobromae*, which, consequently, could mean that this is the only *Lasiodiplodia* species capable of producing compounds of this family (Table 1). The first identified compound of this class is an epoxycyclohexanediol named theobroxide (**1**), which owes its trivial name to its identification in cultures of *L. theobromae* IFO 31059.[28] Although five novel related compounds have subsequently been identified (**2–6**), theobroxide is the only one containing an epoxide group (Fig. 3).

Table 1 List of the cyclohexenols, cyclohexenones and cyclopeptides produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Cyclohexenols and cyclohexenones				
1	Theobroxide	*Lasiodiplodia theobromae* (IFO 31059)	—	28
		L. theobromae (OCS71)	—	29
2	(4*S*,5*S*)-4,5-Dihydroxy-2-methyl-cyclohex-2-enone	*L. theobromae* (OCS71)	—	29
3	(4*R*,5*R*)-4,5-Dihydroxy-3-methylcyclohex-2-enone	*L. theobromae* (OCS71)	—	29
4	(4*S*,5*S*)-4,5-Dihydroxy-3-methylcyclohex-2-enone	*L. theobromae* (OCS71)	—	29 and 31
5	(3a*R*,4*S*,5*R*,7a*S*)-4,5-Dihydroxy-6-methyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-2-one	*L. theobromae* (OCS71)	—	29
		L. theobromae (IFO 31059)	—	30
6	(3a*S*,4*R*,5*S*,7a*R*)-4,5-Dihydroxy-7-methyl-3a,4,5,7a-tetrahydrobenzo[1,3]dioxol-2-one	*L. theobromae* (OCS71)	—	31
Cyclopeptides				
7	Aldsulfin	*Lasiodiplodia pseudotheobromae* (FKI-4499)	Soil	41
8	Cyclo-(D-*N*-OH-Ala, D-Trp)	*Lasiodiplodia chiangraiensis* (MFLUCC21-0003)	Decaying wood	36
9	Cyclo-(Leu–Pro)	*Lasiodiplodia iranensis* (F0619)	*Avicennia germinans*	42
		L. theobromae (AUMC 8903)	*Dracaena draco*	43
		L. theobromae (SNFF)	*Solanum nigrum*	44
		L. theobromae (LA-SOL3, LA-SV1)	*Vitis vinifera*	45
10	Cyclo-(Phe–Pro)	*L. theobromae* (SNFF)	*S. nigrum*	44
		L. theobromae (LA-SOL3, LA-SV1)	*V. vinifera*	45
11	Cyclo-(Trp–Ala)	*L. theobromae* (CAA019 and CBS339.90)	*Cocos nucifera* and human	46
		L. pseudotheobromae (F2)	*Illigera rhodantha*	35
		L. chiangraiensis (MFLUCC21-0003)	Decaying wood	36
12	(3*R*,6*R*)-3-((1*H*-Indol-3-yl)methyl)-1-hydroxy-6-methylpiperazine-2,5-dione	*L. chiangraiensis* (MFLUCC21-0003)	Decaying wood	36
13	Lasiodipline A	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
14	Lasiodipline B	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
15	Lasiodipline C	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
		L. pseudotheobromae (FKI-4499)	Soil	41
16	Lasiodipline D	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
17	Lasiodipline E	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
18	Lasiodipline F	*L. pseudotheobromae* (F2)	*I. rhodantha*	35
19	Lasiodipline G	*L. chiangraiensis* (MFLUCC21-0003)	Decaying wood	36
20	Maculosin	*L. theobromae* (AUMC 8903)	*D. draco*	43
21	Clavatustide C	*L. chiangraiensis*	Decaying wood	36
22	Scopularide A	*L. theobromae*	*Musa paradisiaca*	40

Theobroxide is known for inducing potato micro-tuber formation,[28] and when tested for plant growth regulation on seedlings of *Nicotiana tabacum*, along with some related compounds (**2–4**), it showed inhibitory effects (Table S1).[29] Compounds **5** and **6** possess a further subunit constituted by a five-membered cyclic carbonate, a structural feature not commonly found in secondary metabolites. These two novel theobroxide-related compounds have been isolated from the mycelia and culture filtrates of *L. theobromae* IFO 31059 and OCS71.[29–31]

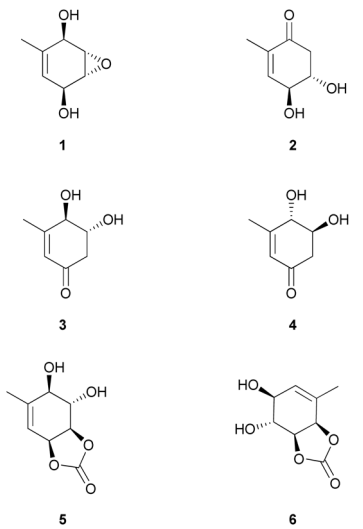

Fig. 3 Chemical structures of the cyclohexenols and cyclohexenones.

2.2 Cyclopeptides

Diketopiperazines are the smallest cyclopeptides obtained by the condensation of two α-amino acids and characterized by a broad structural diversity. These compounds are abundant in nature as products of plants, animals and microorganisms.[32–34] To date, fourteen diketopiperazines have been found in cultures of *Lasiodiplodia* spp. (Table 1 and Fig. 4). (3*R*,6*R*)-3-((1*H*-Indol-3-yl)methyl)-1-hydroxy-6-methylpiperazine-2,5-dione (**12**) and lasiodiplodines A–G (**13–19**, respectively) share the same framework obtained by the condensation of tryptophan and alanine residues, differing in some substituents. In particular, *L. pseudotheobromae* is a good producer of sulfureous diketopiperazines with a di- and tri-sulfide bridge (**7**, **16** and **19**) or

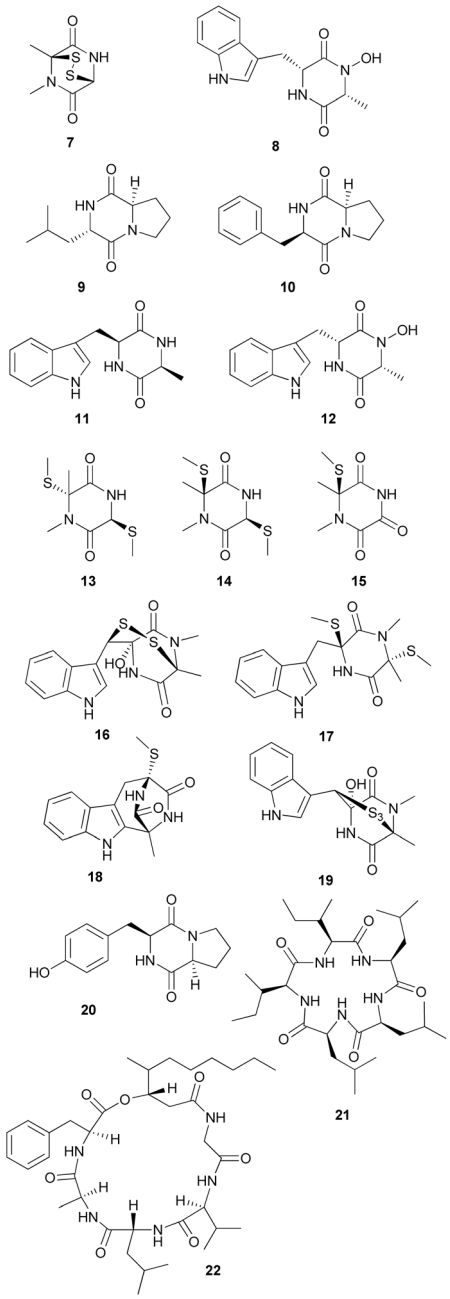

Fig. 4 Chemical structures of the cyclopeptides.

methylthio groups (**13–15**, **17** and **18**). Lasiodipline F (**18**) is a diketopiperazine possessing an unusual skeleton including a characteristic tetracyclic indole unit.[35] Recently, a new thiodiketopiperazine, named lasiodipline G (**19**), has been isolated from cultures of a decaying wood-derived strain of *L. chiangraiensis*.[36] Furthermore, this new compound exhibited significant cytotoxic activities against several cell lines (Table S1). Promising data on the antimicrobial activities of lasiodipline E (**17**) were obtained by Wei *et al.*[35] In fact, **17** was demonstrated to be antibacterial against the clinical strains *Streptococcus* sp., *Bacteroides vulgatus*, *Peptostreptococcus* sp. and *Veillonella parvula* (Table S1).

Clavatustide C (**21**) and scopularide A (**22**) are cyclodepsipeptides, cyclic peptides made up of both proteinogenic and nonproteinogenic amino acids linked by amide and ester bonds.[37] In particular, clavatustide C is a cyclo-(L-Ile–L-Ile–L-Leu–L-Lue–L-Leu) and identified as product of *L. chiangraiensis*. It must be noted that this compound was wrongly reported as clavatustide B in the original paper, but experimental data in the SI confirm the structure of **21**. Thus, its correct trivial name and structure are reported in Table 1 and Fig. 4.[36] Clavatustide C has the same amino acid composition (*i.e.*, two L-Ile and three L-Leu), but a different sequence, as viscumamide, a metabolite produced by the fungus *Paecilomyces* sp.[38] Viscumamide contains the most common cyclic sequence of these five peptide units in which two L-isoleucines are embedded between three L-leucines.[39]

Scopularide A (**22**) is also known as cyclo-(3-hydroxy-4-methyldecanoyl-Gly–L-Val–D-Leu–L-Ala–L-Phe) and has been identified in cultures of *L. theobromae* isolated from *Musa paradisiaca*.[40]

2.3 Depsidones

Depsidones are metabolites that share a conserved 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one ring substituted in different positions with various substituents. These compounds are mostly found in lichens[47–49] and only a few of them have been isolated from non-lichen sources.[50,51] Five previously undescribed depsidones, such as botryorhodines A–D and I (**23–27**), have been isolated from cultures of *L. theobromae*, along with 3,8-dihydroxy-4-(methoxymethyl)-1,6-dimethyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one (**28**) and simplicildone A (**29**) (Table 2), which had been previously reported from a marine derived fungus[52] and from the endophytic fungus *Simplicillium* sp.,[53] respectively.

As can be seen in Fig. 5, depsidones produced by *L. theobromae* share the same basic framework but differ in some substituents (*i.e.* methyl and hydroxyl groups) on the phenyl moieties (**23–27**).[54–57]

2.4 Exopolysaccharides

Bacteria and fungi are known to produce extracellular polysaccharides with different structural complexities.[58,59] Exopolysaccharides exhibit peculiar structural features, including monosaccharide composition, type and configuration of glycosidic linkages, number of residues, and degree of branching. These biopolymers play diverse roles in the life cycle of producing microorganisms. In particular, exopolysaccharides provide protection to microbial cells during infection, confer tolerance to various antimicrobial agents and are involved in biofilm formation.[60]

Some *Lasiodiplodia* spp. have been identified as exopolysaccharide producers (Table 2). Lasiosan (**30**) is a glucomannan produced by a strain of *Lasiodiplodia* sp. isolated from a spoiled banana sample. The component sugars of lasiosan are β-(1→4)-linked D-mannose and D-glucose in a ratio of 1 : 1.[61] Some strains of *L. theobromae* biosynthesize lasiodiplodan, an exocellular (1→6)-β-glucan existing in a triple-helix conformation (Fig. 6).[62,63] Lasiodiplodan (**31**) is an unusual glucan, as it is

Table 2 List of the depsidones and exopolysaccharides produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Depsidones				
23	Botryorhodine A	*Lasiodiplodia theobromae* (TBRC 15112)	*Achyranthes aspera*	54
		L. theobromae (BPPCA 144)	*Aglaia argentea*	55
		L. theobromae	*Bidens pilosa*	56
		L. theobromae (M4.2-2)	Mangrove sediment	57
24	Botryorhodine B	*L. theobromae*	*B. pilosa*	56
		L. theobromae (M4.2-2)	Mangrove sediment	57
25	Botryorhodine C	*L. theobromae*	*B. pilosa*	56
26	Botryorhodine D	*L. theobromae*	*B. pilosa*	56
		L. theobromae (M4.2-2)	Mangrove sediment	57
27	Botryorhodine I	*L. theobromae* (M4.2-2)	Mangrove sediment	57
28	3,8-Dihydroxy-4-(methoxymethyl)-1, 6-dimethyl-11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one	*L. theobromae* (M4.2-2)	Mangrove sediment	57
29	Simplicildone A	*L. theobromae* (M4.2-2)	Mangrove sediment	57
Exopolysaccharides				
30	Lasiosan	*Lasiodiplodia* sp. (B2)	*Musa paradisiaca*	61
31	Lasiodiplodan	*L. theobromae* (CCT3966)	—	67
		L. theobromae (MMPI)	*Annona squamosa*	62, 63 and 68
		L. theobromae (MMBJ)	—	69
32	Botryosphaerans	*L. theobromae* (MAMB-05)	—	66 and 70–72
		L. theobromae (RCYU 30101)	—	73
		L. theobromae	—	65
		L. theobromae (DABAC-P82)	—	74

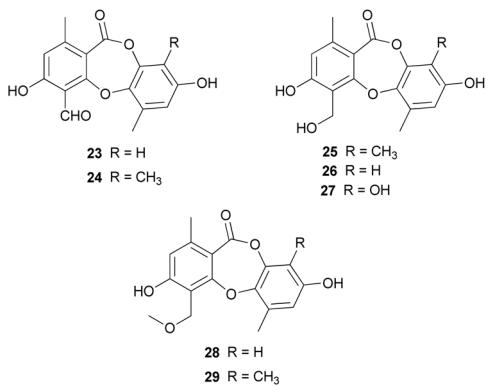

Fig. 5 Chemical structures of the depsidones.

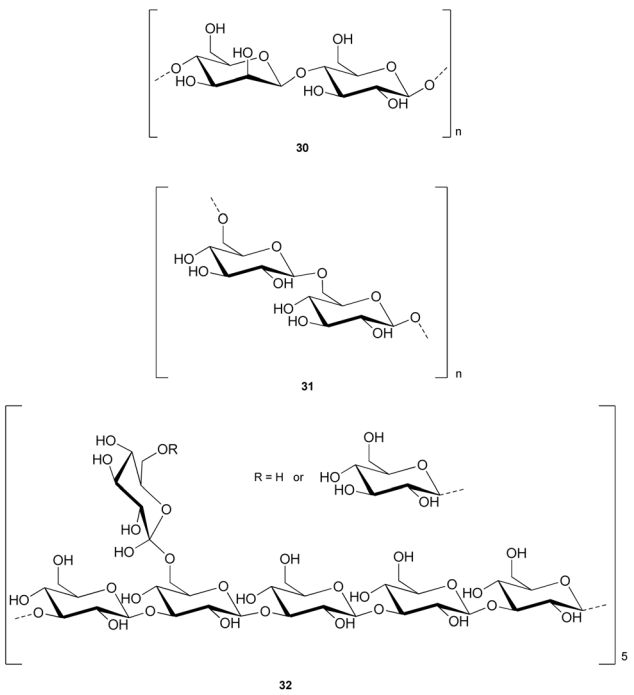

Fig. 6 Chemical structures of the exopolysaccharides.

a linear (1→6)-β-D-glucan, whereas glucans are mainly of the (1→3)-β type (Fig. 6).[64] A comparison of the fermentative parameters of *L. theobromae* MMPI to evaluate the lasiodiplodan yield showed that the maximum production can be obtained in agitated flasks with urea as the nitrogen source and glucose or maltose as the carbon source.[62]

Unlike **30** and **31**, botryosphaerans (**32**) are branched exopolysaccharides produced by *L. theobromae*. The structure of the first botryosphaeran isolated was characterised as a (1→3; 1→6)-β-D-glucan, with approximately 22% side branching comprising single (1→6)-β-linked glucosyl and (1→6)-β-linked diglucosyl residues (Fig. 6). Comparing botryosphaeran production by *L. theobromae* on diverse carbon sources, it was observed that the carbon source affected the side chain structures, but not the main chain constitution of **32**. Indeed, botryosphaerans have the same backbone composed of glucopyranosyl units (1→3)-linked and substituted at *O*-6 by glucosyl and diglucosyl units, but when the fungus was grown on fructose, the produced exopolysaccharide had 31% side-branching, a branch point to every three glucose units in the main chain,

Table 3 List of the fatty acids, fatty acid esters, indoles, isocoumarins and 3,4-dihydroisocoumarins produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Fatty acids and fatty acids esters				
33	Hexadecanoic acid (palmitic acid)	*Lasiodiplodia citricola* (ALG111 and ALG34)	*Citrus sinensis*	84
		Lasiodiplodia theobromae (CBS 122127 and 2334)	—	96
34	9-Hydroxy-10-oxo-12*Z*,15*Z*-octadecadienoic acid	*Lasiodiplodia theobromae* (CBS 122127 and 2334)	—	96
35	Methyl hexadecanoate	*L. theobromae* (UCD256Ma and MXL28)	*Vitis vinifera*	81
		Lasiodiplodia pseudotheobromae (IBRL OS-64)	*Ocimum sanctum*	97
36	Ethyl hexadecanoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
37	2-Methylpropyl hexadecanoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
38	Bis 2-ethylhexyl hexanedioate	*L. pseudotheobromae* (IBRL OS-64)	*O. sanctum*	97
39	Octadecanoic acid (stearic acid)	*L. theobromae* (CBS 122127)	—	96
		L. pseudotheobromae (APR5)	*Andrographis paniculata*	98
40	Methyl octadecanoate	*L. pseudotheobromae* (IBRL OS-64)	*O. sanctum*	97
41	(*Z*)-9-Octadecenoic acid (oleic acid)	*L. theobromae* (CBS 122127)	—	96
		L. pseudotheobromae (APR5)	*A. paniculata*	98
42	9-Methyl (*Z*)-9-octadecenoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
43	Ethyl octadecanoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
44	Ethyl (*Z*)-9-octadecenoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
45	Ethyl (*E*)-9-octadecenoate	*L. theobromae* (UCD256Ma)	*V. vinifera*	81
46	9,12-Octadecadienoic acid (linoleic acid)	*L. theobromae* (CBS 122127 and 2334)	—	96
		L. citricola (ALG111, ALG39, ALG81 and ALG34)	*C. sinensis*	84
47	Methyl (*Z*,*Z*)-9,12-octadecadienoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
48	Ethyl-(*Z*,*Z*)-9,12-octadecadienoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
49	(*Z*,*Z*,*Z*)-9,12,15-Octadecatrienoic acid (linolenic acid)	*L. citricola* (ALG111 and ALG39)	*C. sinensis*	84
50	Eicosanoic acid	*L. theobromae* (CBS 122127)	—	96
51	Ethyl-(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoate	*L. theobromae* (UCD256Ma and MXL28)	*V. vinifera*	81
Indoles				
52	Indole	*L. theobromae* (LA-SOL3, LA-SV1)	*V. vinifera*	45
53	Indole-3-acetic acid	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
		L. citricola (ALG111)	*C. sinensis*	84
54	Indole-3-butyric acid	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
55	Indole-3-carbaldehyde	*L. pseudotheobromae* (LPS-1)	*Ilex cornuta*	99
		L. theobromae (LA-SOL3, LA-SV1)	*V. vinifera*	45
		L. theobromae	—	100
		L. theobromae (SNFF)	*Solanum nigrum*	44
56	Indole-3-carboxylic acid	*L. theobromae* (CAA019, CBS339.90)	*Cocos nucifera* and human	46
		L. theobromae (LA-SOL3, LA-SV1)	*V. vinifera*	45 and 101
		L. pseudotheobromae (LPS-1)	*I. cornuta*	99
		L. theobromae	*Bidens pilosa*	56
		L. theobromae	—	100
		L. theobromae (CSS01s)	*V. vinifera*	102
		Lasiodiplodia chiangraiensis (MFLUCC21-0003)	Decaying wood	36
		L. citricola (ALG111 and ALG39)	*C. sinensis*	84
		Lasiodiplodia sp.	*Handroanthus impetiginosus*	103
57	Indole-3-propionic acid	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
Isocoumarins and 3,4-dihydroisocoumarins				
58	(−)-Mellein	*L. theobromae* (BPPCA 144)	*Aglaia argentea*	55
		Lasiodiplodia laeliocattleyae (CMM0206)	*V. vinifera*	104
		L. theobromae (MJ2211)	*Vitex pinnata*	105
		L. theobromae (LA-SOL3, LA-SV1)	*V. vinifera*	45 and 101
		L. theobromae (GK-1)	*C. nucifera*	106
		L. theobromae (M4.2-2)	*Mangrove sediment*	57
		Lasiodiplodia euphorbiaceicola (CMM0181)	*V. vinifera*	107
		L. theobromae (PSU-M35)	*Garcinia mangostana*	108
		L. theobromae	—	100
		L. theobromae (IFO 31059)	—	28
		L. pseudotheobromae (C1136)	*Tridax procumbus*	109
		L. venezuelensis (A02EtM)	*Astrocaryum sciophilum*	95
		L. theobromae (SJF-1)	*Syzygium cumini*	93
		L. theobromae (TBRC 15112)	*A. aspera*	54
		L. citricola (ALG111, ALG39, ALG81 and ALG34)	*C. sinensis*	84
		L. theobromae (NSTRU-PN1.4)	Soil	110

Table 3 (*Contd.*)

No.	Compound	Fungal producer (strain)	Source	Ref.
59	(−)-(3*R*,4*R*)-4-Hydroxymellein	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera* and human	46
		L. theobromae (LA-SOL3 and LA-SV1)	*V. vinifera*	45 and 101
		L. theobromae (#009)	*Psidium guajava*	111
		L. euphorbiaceicola (CMM0181)	*V. vinifera*	107
		L. theobromae (PSU-M35)	*G. mangostana*	108
		L. theobromae	—	100
		L. venezuelensis (A02EtM)	*A. sciophilum*	95
		L. citricola (ALG111, ALG39, ALG81 and ALG34)	*C. sinensis*	84
60	(−)-(3*R*,4*S*)-4-Hydroxymellein	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera* and human	46
		L. euphorbiaceicola (CMM0181)	*V. vinifera*	107
		L. theobromae (PSU-M35)	*G. mangostana*	108
		L. venezuelensis (A02EtM)	*A. sciophilum*	95
		Lasiodiplodia sp.	*H. impetiginosus*	103
61	(−)-(3*R*)-5-Hydroxymellein	*L. theobromae* (PSU-M35)	*G. mangostana*	108
62	(+)-(3*R*,4*S*)-4,5-Dihydroxymellein	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
63	Orthosporin	*L. theobromae*	*Musa paradisiaca*	112
64	Citreoisocoumarinol	*L. theobromae*	*M. paradisiaca*	40

while when the carbon source was sucrose, the obtained exopolysaccharide was less branched (21%), with a branch point for every five glucosyl residues in the main chain. The result obtained from *L. theobromae* grown on sucrose is very similar to the one obtained when the fungus was grown on glucose (22% side branching).[65,66] The production of exopolysaccharides by *Lasiodiplodia* spp. is particularly relevant because these compounds were found to be significantly active during *in vivo* assays (Fig. S1).

2.5 Fatty acids and fatty acid esters

A variety of free fatty acids and naturally occurring esters of fatty acids was identified in cultures of *Lasiodiplodia* spp. (Table 3). Some of them are very common, such as palmitic acid (**33**) and oleic acid (**41**), which are the most common saturated and unsaturated fatty acids, respectively, found in animals, plants and microorganisms (Fig. 7).[75–77] Fatty acids are typically considered primary metabolites, as they are essential for the growth, development, and reproduction of living organisms.[78] However, in *Lasiodiplodia* spp., they may also act as secondary metabolites, particularly when involved in plant–fungus interactions. In fact, the high quantities and the wide variety of fatty acids produced by *Lasiodiplodia* spp. might be linked to the capacity of these fungi to infect a broad host range. Fatty acids and modified fatty acids play a pivotal role in plant–microbe interactions, serving diverse functions, such as signalling and virulence factors.[79] Furthermore, fatty acids represent the

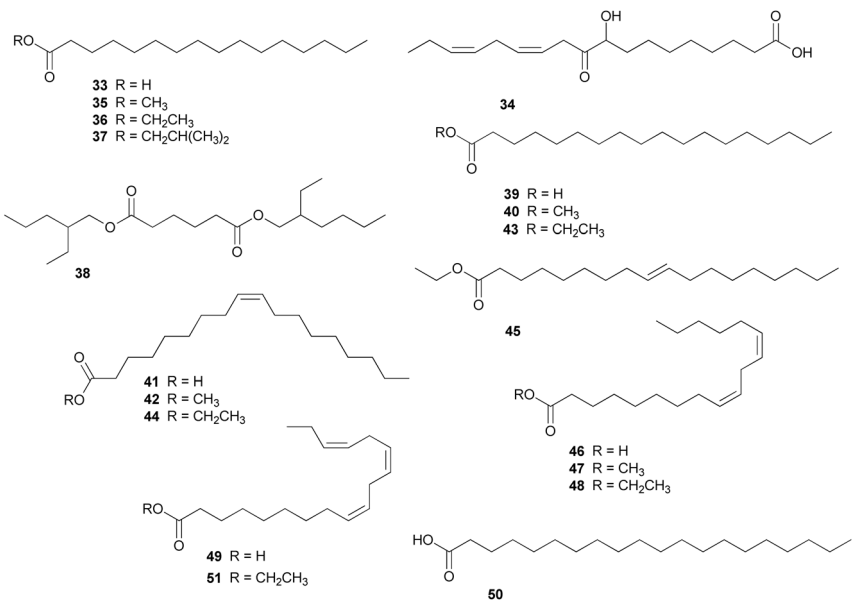

Fig. 7 Chemical structures of the fatty acids and fatty acid esters.

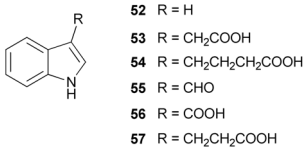

Fig. 8 Chemical structures of the indoles.

starting material for many secondary metabolites involved in fungal virulence, such as jasmonates.[80]

Investigations conducted on cultures of *L. theobromae* strains isolated in California, Mexico showed a high production and a wide variety of fatty acids and their esters with significant effects on tobacco plants.[81] In fact, fatty acids could be considered plant growth regulators due to their ability to affect tobacco germination and early growth (Table S1).

The lipid metabolism of *L. theobromae* seems to be affected by nutrient availability. Indeed, when testing different carbon sources, the production of different fatty acids was observed, which could have implications for pathogenicity.[81,82]

2.6 Indoles

Indole represents the scaffold of a large family of organic compounds comprising over a thousand members. In fact, several natural products exhibit highly complex structures characterised by an indole nucleus.[83] Six indoles, including the parent compound of this class of metabolites, have been identified in cultures of *Lasiodiplodia* spp. (Table 3 and Fig. 8). Although indoles have wide structural diversity, those produced by *Lasiodiplodia* spp. are very simple, featuring an additional group at C-3 of the pyrrole ring. Among them, indole 3-carboxylic acid (**56**) is the most common in *Lasiodiplodia* spp. cultures. Besides this compound, *Lasiodiplodia citricola* and *L. theobromae* also produce indole 3-acetic acid (**53**), the most studied plant hormone belonging to the auxin class.[84,85]

2.7 Isocoumarins and 3,4-dihydroisocoumarins

Isocoumarin is a heterocyclic compound and a key structural motif of a large group of natural products. These compounds comprise a α-pyranone condensed with one aromatic ring and are structural isomers of coumarins (Table 3).

3,4-Dihydroisocoumarins are a subgroup of isocoumarins, also named melleins like their parent compound, *i.e.* (−)-mellein. (−)-Mellein (**58**) was first reported in 1933 as a product of *Aspergillus melleus*,[86] and subsequently this compound and its derivatives have been frequently found in fungal species such as *Cladosporium*,[87] *Fusarium*[88] and *Penicillium*[89,90] as well as several botryosphaeriaceous species.[26,27,91,92] (−)-Mellein was extensively studied for its bioactivities, showing promising results as an antimicrobial agent (Table S1).[93]

(+)-(3*R*,4*S*)-4,5-Dihydroxymellein (**62**) has been reported from *L. venezuelensis* isolated from *Astrocaryum sciophilum* palm tree leaves.[94,95] However, there is an inaccuracy in the study by Pellissier *et al.*[94] in 2021, because the authors reported in their paper the structure of its diastereomer (*i.e.* (+)-(3*R*,4*R*)-4,5-dihydroxymellein). After checking the data reported in the manuscript,[94] we can conclude that (+)-(3*R*,4*S*)-4,5-dihydroxymellein was detected and the correct structure is reported in Fig. 9.

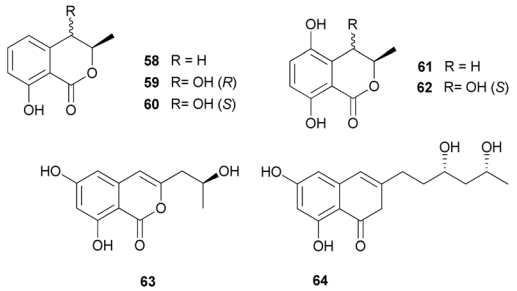

Fig. 9 Chemical structures of the isocoumarins and 3,4-dihydroisocoumarins.

2.8 Jasmonates

Jasmonates are an important subgroup of oxylipins derived from linolenic acid, including the free acid and several conjugates, which are signalling molecules produced by plants and fungi. (−)-Jasmonic acid (**65**, 3-oxo-2-(2′-pentenyl)-cyclopentaneacetic acid) is the basic structure of this naturally occurring family of compounds, which is characterized by a cyclopentanone ring with a pentenyl and a carboxylic acid side chain. This compound occurs in the essential oils of *Jasminum grandiflorum* along with its methyl ester (**66**).[113] Even if jasmonates are particularly known as plant hormones involved in development processes, Aldridge *et al.* in 1971 first isolated (−)-jasmonic acid from *L. theobromae*.[100] Subsequently, several findings have confirmed that numerous species of *Lasiodiplodia* are capable of synthesizing compounds belonging to this class (Table 4). This could be the result of a phenomenon frequently observed in the genomes of prokaryotes and eukaryotes named horizontal gene transfer. It is defined as the exchange and stable integration of genetic material among phylogenetically distant species, which could significantly impact their metabolic capabilities.[114,115] Indeed, comparative genomic and transcriptomic studies on genome evolution and the origin of pathogenicity in botryosphaeriaceous fungi demonstrated the role of genome expansion and horizontal gene transfer in the evolutionary adaptation of Botryosphaeriaceae.[116,117]

The production of (−)-jasmonic acid by numerous strains of *L. theobromae* has been optimized, showing promising high yields of this compound in fermentation medium.[85,118–122]

As reported in Fig. 10, 4,5-didehydro-7-iso-jasmonic acid (**81**) is the only jasmonate produced by *Lasiodiplodia* spp. presenting a cyclopentenone ring. In general, jasmonic acid derivatives exhibit modifications on their side chains. For instance, six hydroxylated derivatives on the pentenyl side chain have been reported from *L. theobromae*.[119,123–125]

In plants, (−)-jasmonic acid frequently occurs conjugated with sugars and with a variety of amino acids (*e.g.* isoleucine, leucine, valine, alanine, tyrosine, and phenylalanine). Isoleucine is the principal amino acid linked to (−)-jasmonic acid,

Table 4 List of the jasmonates, lactones and lactols produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Jasmonates				
65	(−)-Jasmonic acid	*Lasiodiplodia theobromae*	*Mangifera indica*, *Cocos nucifera*, *Passiflora edulis*, *Carica papaya*, *Paullinia cupana*, and *Theobroma cacao*	122
		L. theobromae (2334, 1517 and 83)	*Citrus cinensis*, wood	85
		L. theobromae	*Rosa* species	132
		L. theobromae (CAA019 and CBS339.90)	*C. nucifera* and human	46
		L. theobromae (LA-SOL3, LA-SV1)	*Vitis vinifera*	45 and 101
		Lasiodiplodia mediterranea (B6)	*V. vinifera*	131
		Lasiodiplodia sp. (BL 101)	*V. vinifera*	129
		Lasiodiplodia pseudotheobromae (LPS-1)	*Ilex cornuta*	99
		Lasiodiplodia brasiliense (CMM0418)	*V. vinifera*	107
		Lasiodiplodia crassispora (CMM0390)	*V. vinifera*	107
		Lasiodiplodia iranensis (CMM0840)	*V. vinifera*	107
		Lasiodiplodia pseudotheobromae (CMM0204)	*V. vinifera*	107
		L. theobromae (D 7/2)	*Citrus sinensis*	123–125
		L. theobromae	—	100
		L. theobromae (IFO 31059)	—	28
		L. theobromae (CSS01s)	*V. vinifera*	102
		L. iranensis (CCTCC no. M2017288)	*Barringtonia racemosa*	133 and 134
66	Methyljasmonate	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
67	*cis*-Jasmone	*L. theobromae* (MAFF no. 306027)	—	135
68	(11*R*)-(−)-Hydroxyjasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
69	(11*S*)-(−)-Hydroxyjasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
		L. theobromae (2334)	*Helianthus annuus*	119
70	8-Hydroxy-jasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
71	12-Hydroxy-jasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
		L. theobromae (2334)	*H. annuus*	119
72	3-Oxo-2-(1-hydroxy-2*Z*-pentenyl) cyclopent-1-yl-butyric acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
73	3-Oxo-2-(4-hydroxy-2*Z*-pentenyl) cyclopent-1-yl-butyric acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
74	Jasmonic acid–glycine	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
75	Jasmonic acid–isoleucine	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
76	Jasmonic acid–serine	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
77	Jasmonic acid–threonine	*Lasiodiplodia iranensis* (F0619)	*Avicennia germinans*	42
		L. theobromae (2334 and 1517)	*C. cinensis* and wood	85
78	(+)-7-iso-Jasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
79	Ethyl (+)-7-iso-jasmonate	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
80	(+)-9,10-Dihydro-7-iso-jasmonic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
81	4,5-Didehydro-7-iso-jasmonic acid	*L. iranensis* (F0619)	*A. germinans*	42
		L. theobromae (D 7/2)	*C. sinensis*	123–125
82	11,12-Didehydro-7-iso-jasmonic acid	*L. iranensis* (F0619)	*A. germinans*	42
		L. theobromae (D 7/2)	*C. sinensis*	123–125
83	(1*S*,2*S*)-[3-Oxo-2-(2*Z*-pentenyl)-cyclopentyl]butanoic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
		L. theobromae (2334)	*H. annuus*	119
84	(1*R*,2*S*)-[3-Oxo-2-(2*Z*-pentenyl)-cyclopentyl]propanoic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
85	(+)-Cucurbic acid	*L. theobromae* (D 7/2)	*C. sinensis*	123–125
86	Lasiojasmonate A	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
87	Lasiojasmonate B	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
88	Lasiojasmonate C	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
Lactones and lactols				
89	(−)-Botryodiplodin	*L. theobromae*		20
		L. theobromae (LA-SOL3 and LA-SV1)	*V. vinifera*	45 and 101
		L. theobromae	*C. nucifera*	136
		Lasiodiplodia sp. (BL 101)	*V. vinifera*	129
90	3-*epi*-Botryodiplodin	*L. theobromae* (LA-SOL3 and LA-SV1)	*V. vinifera*	101
91	(3*R*,4*S*)-4-Acetyl-3-methyldihydrofuran-2(3*H*)-one	*L. theobromae* (LA-SOL3 and LA-SV1)	*V. vinifera*	101

Table 4 (*Contd.*)

No.	Compound	Fungal producer (strain)	Source	Ref.
92	(3*S*,4*S*)-4-Acetyl-3-methyldihydrofuran-2(3*H*)-one	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera*, and human	46
		L. theobromae (LA-SOL3 and LA-SV1)	*V. vinifera*	101
		L. theobromae (PSU-M35)	*Garcinia mangostana*	108
93	(3*R*,4*R*)-4-Acetyl-3-methyl-2(3*H*)-dihydrofuranone	*L. theobromae* (NSTRU-PN1.4)	Soil	110
94	Nigrosphaerilactone (3*S*,4*R*,5*R*)-4-(hydroxymethyl)-3,5-dimethyldihydrofuran-2(3*H*)-one	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera* and human	46
		L. theobromae (LA-SOL3 and LA-SV1)	*V. vinifera*	101
		L. mediterranea (B6)	*V. vinifera*	131
		Lasiodiplodia sp. (BL 101)	*V. vinifera*	129
		L. pseudotheobromae (#1048AMSTYEL)	*Aegle marmelos*	137
		L. theobromae (PSU-M35)	*G. mangostana*	108
		L. theobromae (NSTRU-PN1.4)	Soil	110
95	Botryosphaerilactone A	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera* and human	46
		Lasiodiplodia sp. (BL 101)	*V. vinifera*	129
		L. theobromae (PSU-M35)	*G. mangostana*	108
		L. theobromae (NSTRU-PN1.4)	Soil	110
96	Botryosphaerilactone B	*L. theobromae* (PSU-M35)	*G. mangostana*	108
		L. theobromae (NSTRU-PN1.4)	Soil	110
97	Botryosphaerilactone C	*L. theobromae* (PSU-M35)	*G. mangostana*	108
		L. theobromae (NSTRU-PN1.4)	Soil	110
98	Botryosphaerilactone D	*L. theobromae* (NSTRU-PN1.4)	Soil	110
99	Botryosphaerilactone E	*L. theobromae* (NSTRU-PN1.4)	Soil	110
100	16-*O*-Acetylbotryosphaerilactone A	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
101	16-*O*-Acetylbotryosphaerilactone C	*Lasiodiplodia* sp. (BL 101)	*V. vinifera*	129
102	Lasiolactol A	*L. theobromae* (LA-SOL3 and LA-SV1)	*V. vinifera*	101
		L. mediterranea (B6)	*V. vinifera*	131
103	Lasiolactol B	*L. theobromae* (LA-SOL3 and LA-SV1)	*V. vinifera*	101
		L. mediterranea (B6)	*V. vinifera*	131
104	(3*S*,4*R*)-3-Carboxy-2-methylene-heptan-4-olide	*L. theobromae*	*M. indica*	138
		L. venezuelensis (A02EtM)	*Astrocaryum sciophilum*	95
		Lasiodiplodia sp.	*Handroanthus impetiginosus*	103
105	Decumbic acid	*L. theobromae*	*M. indica*	138
		L. venezuelensis (A02EtM)	*A. sciophilum*	95
		Lasiodiplodia sp.	*H. impetiginosus*	103
106	Decumbic acid B	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
107	Lasiolactone (*R*)-(−)-2-octeno-D-lactone	*L. theobromae* (GK-1)	*C. nucifera*	106
		L. theobromae (PSU-M114)	*G. mangostana*	108
108	Lasdiplactone	*L. pseudotheobromae* (#1048AMSTYEL)	*Aegle marmelos*	137
109	Massoialactone	*L. theobromae* (GK-1)	*C. nucifera*	106
110	Tetrahydro-4-hydroxy-6-propylpyran-2-one	*L. theobromae* (PSU-M114)	*G. mangostana*	108
111	(4*R**,6*R**)-4-Hydroxy-6-*N*-propyl-1-oxacyclo-hexan-2-one	*L. theobromae* (BPPCA 144)	*Aglaia argentea*	55
112	(5*S*,6*S*)-6-((3′*S*,4′*S*,*Z*)-3′,4′-Dihydroxypent-1-en-1-yl)-5-hydroxy-5,6-dihydro-2*H*-pyran-2-one	*L. venezuelensis*	*A. sciophilum*	94
113	Pantolactone	*L. pseudotheobromae* (APR5)	*A. paniculata*	98
114	Monocerin	*L. theobromae* (AUMC 8903)	*D. draco*	43
115	Dihydrocumambrin A	*L. theobromae* (AUMC 8903)	*D. draco*	43
116	Lasiodione A	*Lasiodiplodia* sp. (AD-2102)	*Artemisia desertorum*	139
117	3-Methyl-3,4-dihydro-1*H*-isochromene-1,8(7*H*)-dione	*L. theobromae*	*Peronema canescens*	140
118	3-Hydroxy-4(hydroxy(4-hydroxyphenyl) methyl)-γ-butyrolactone	*L. theobromae*	*P. canescens*	140
119	Diplobifuranylone B	*L. venezuelensis*	*A. sciophilum*	94
120	3ξ-(1ξ-Hydroxyethyl)-7-hydroxy-1-isobenzofuranone	*L. venezuelensis*	*A. sciophilum*	94

while other amino acids rarely occur in conjugated form.[126–128] The production of glucose or gentiobiose esters of jasmonic acid by *Lasiodiplodia* spp. has not yet been reported, while the presence of jasmonic acid–glycine, jasmonic acid–isoleucine, jasmonic acid–serine and jasmonic acid–threonine conjugates (**74–77**) has been reported in fermentation broths of *L.*

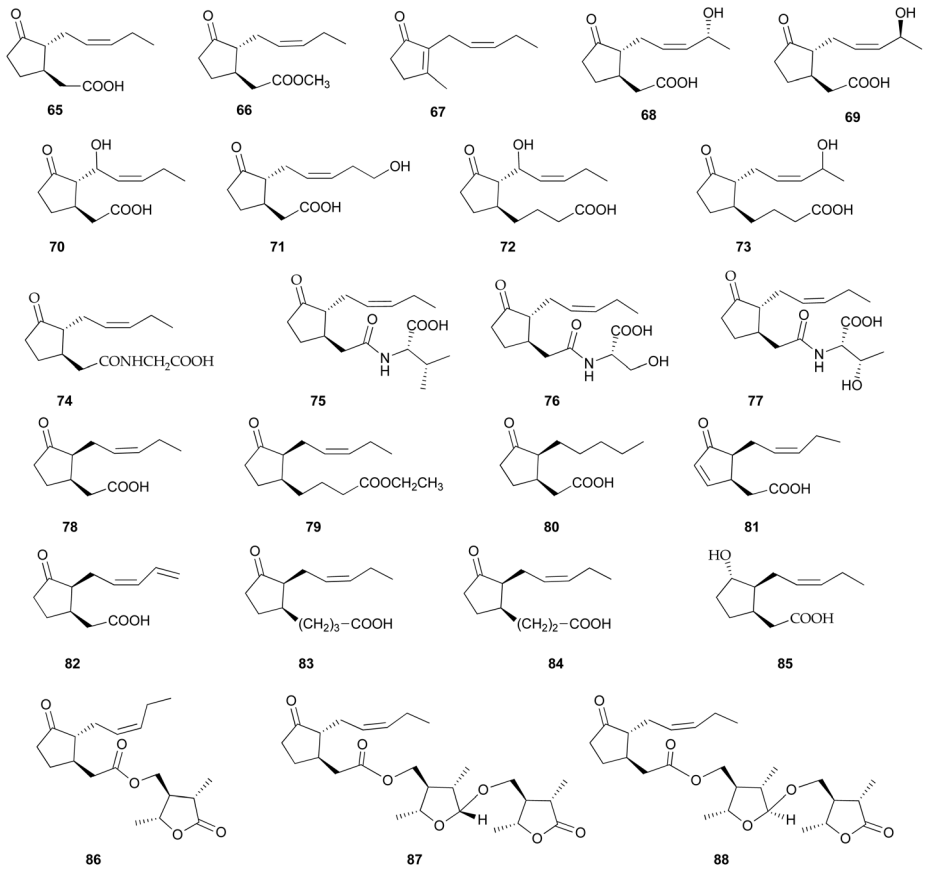

Fig. 10 Chemical structures of the jasmonates.

theobromae isolated from *Citrus cinensis* and wood of Brazilian Amazonia (Table 4).[85]

Interestingly, although jasmonates are primarily plant metabolites, some of them have not been isolated from plants before but have only been detected as fungal products. This is the case of lasiojasmonates, three (−)-jasmonic acids esterified with lactone/lactol subunits (**86–88**), isolated from culture filtrates of a pathogenic strain of *Lasiodiplodi*a sp.[129]

2.9 Lactones and lactols

Lactones and lactols, as reported in Table 4, are a large group of natural polyketides. These compounds are γ- and δ-lactones and lactols.

(−)-Botryodiplodin (**89**) is the first compound belonging to this series isolated from *Lasiodiplodia* spp. and as reported above, it is also the first secondary metabolite isolated from fungi belonging to this genus. This compound attracted the attention of researchers due to its good antimicrobial activity against several fungal and bacterial strains (Table S1).[20] (−)-Botryodiplodin is a hemiacetal and it is reported as epimeric equilibrium at carbon one.[92] Furthermore, *epi*-botryodiplodin (**90**) is the epimeric form of **89** on C-3 isolated for the first time as a natural product from *L. theobromae* associated with grapevine.[101]

Some compounds reported in Fig. 11 are dimeric structures constituted by two subunits of lactones or lactols. Botryosphaerilactones (**95–99**) are five dimeric γ-lactones isolated from strains of *L. theobromae*.[108,110] Furthermore, the acetyl derivatives of botryosphaerilactones A and C (**95** and **97**, respectively) were detected from a strain of *Lasiodiplodia* sp. isolated from grapevine.[129] Nigrosphaerilactone (**94**) is produced by several fungi[130] including different *Lasiodiplodia* spp. (Table 4). This compound has been recently named nigrosphaerilactone, following its discovery as a product of *Nigrospora sphaerica*.[130] For this reason, in many papers it appears with its IUPAC name: (3*S*,4*R*,5*R*)-4-(hydroxymethyl)-3,5-dimethyldihydrofuran-2(3*H*)-one.

Lasiolactols (**102** and **103**) are two dimeric γ-lactols identified in cultures of *L. mediterranea*[131] and closely structurally related to botryosphaerilactones A and C (**95** and **97**, respectively).

2.10 2-(2-Phenylethyl)chromones

2-(2-Phenylethyl)chromones consist of an oxygen-containing heterocycle with a benzoannelated γ-pyrone moiety linked to a phenylethyl residue. These compounds present various substituents, such as hydroxy, methoxy, and chloro groups, on different positions, which endow them with extensive structural variability.[141,142] 2-(2-Phenylethyl)chromones are key

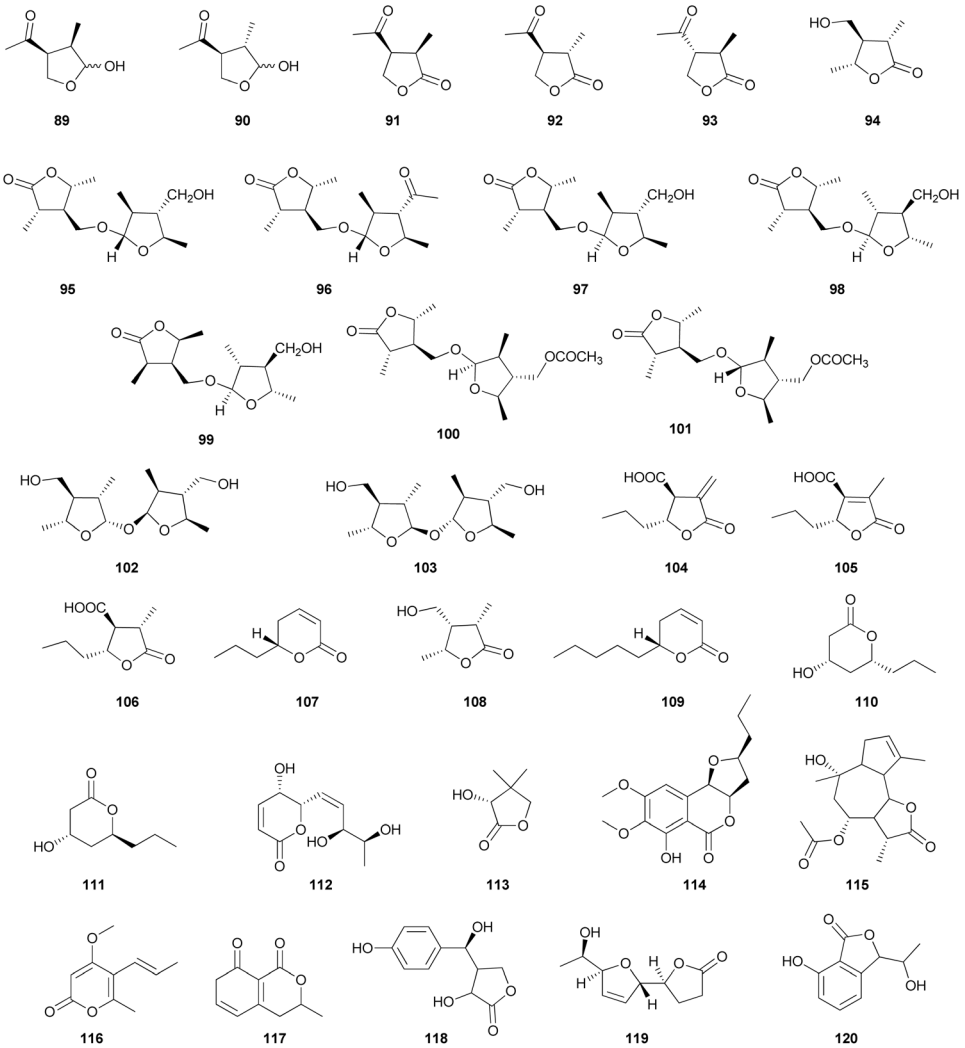

Fig. 11 Chemical structures of the lactones and lactols.

components in agarwood, a resinous material collected from *Aquilaria* trees and used as incense and in Asian traditional medicines.[141] In fact, more than two hundred 2-(2-phenylethyl) chromone derivatives have been isolated and identified from *Aquilaria* spp. Interestingly, seven known 2-(2-phenylethyl) chromone analogues (**121–127**) have been isolated from a solid culture of an endophytic strain of *L. theobromae* from *Aquilaria sinensis* (Table 5 and Fig. 12).[143]

Given the economic importance of agarwood constituents, the production of *Aquilaria* metabolites by an endophytic strain represents a valuable discovery.

2.11 Phenyl and phenol derivatives

The list of phenyl and phenol derivatives produced by *Lasiodiplodia* spp. includes some well-known natural compounds. Phenyl and phenol derivatives are characterized by having at least one aromatic ring which, in the case of phenol derivatives, is functionalized to one or more hydroxyl groups. These compounds range from simple, low molecular-weight compounds to larger, more complex structures.[144,145] These compounds are widespread throughout the plant kingdom,[146,147] but several reports describe their occurrence as fungal products. As can be seen in Table 5 and Fig. 13, *Lasiodiplodia* spp. produce mostly phenol derivatives with simple structures that include a single aromatic group linked to diverse substituents. Due to its wide spectrum of bioactivities, tyrosol (**129**) holds a place of particular relevance among phenolic compounds. From a structural viewpoint, **129** is characterized by a hydroxyethyl chain at the para position of the phenol ring. It is the most abundant phenolic compound in olive oils and wine and described as a health-promoting compound due to its beneficial properties.[148–151] Several species of *Lasiodiplodia* biosynthesize tyrosol and some of them are fungi associated with grapevine.[45,101,104,107] From a strain of *L. theobromae* isolated from *Achyranthes aspera*,[54] tyrosol has been isolated together with two other phenol derivatives, 4-hydroxyphenylacetic acid (**133**) and *N*-(4-hydroxyphenyl)acetamide (**141**). 4-Hydroxyphenylacetic acid has been wrongly reported by the authors as *N*-(4-hydroxyphenyl)acetic acid, hence its correct structure and name have been added in Table 5 and Fig. 13.

Table 5 List of the 2-(2-phenylethyl)chromones, phenyl and phenol derivatives produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
2-(2-Phenylethyl)chromones				
121	6-Hydroxy-7-methoxy-2-(2-phenylethyl)chromone	*Lasiodiplodia theobromae* (A13)	*Aquilaria sinensis*	143
122	6,7-Dimethoxy-2-(2-phenylethyl)chromone	*L. theobromae* (A13)	*A. sinensis*	143
123	(5*S*,6*R*,7*S*,8*R*)-2-(2-Phenylethyl)-5,6,7,8-tetrahydrochromone	*L. theobromae* (A13)	*A. sinensis*	143
124	6-Hydroxy-2-(2-phenylethyl)chromone	*L. theobromae* (A13)	*A. sinensis*	143
125	4-Hydroxy-2-(2-phenylethyl)chromone	*L. theobromae* (A13)	*A. sinensis*	143
126	6-Methoxy-2-phenethyl-4*H*-chromen-4-one	*L. theobromae* (A13)	*A. sinensis*	143
127	6-Methoxy-2-(4-methoxyphenethyl)-4*H*-chromen-4-one	*L. theobromae* (A13)	*A. sinensis*	143
Phenyl and phenol derivatives				
128	Phenol	*Lasiodiplodia pseudotheobromae* (APR5)	*Andrographis paniculata*	98
129	Tyrosol	*L. theobromae* (BPPCA 144)	*Aglaia argentea*	55
		Lasiodiplodia laeliocattleyae (CMM0206)	*Vitis vinifera*	104
		L. theobromae (LA-SOL3 and LA-SV1)	*V. vinifera*	45 and 101
		Lasiodiplodia sp.	*Handroanthus impetiginosus*	154
		Lasiodiplodia euphorbiaceicola (CMM0181)	*V. vinifera*	107
		Lasiodiplodia hormozganensis (CMM0126)	*V. vinifera*	107
		L. theobromae (TBRC 15112)	*Achyranthes aspera*	54
		Lasiodiplodia citricola (ALG111 and ALG81)	*Citrus sinensis*	84
130	2-Phenylethanol	*L. theobromae* (BPPCA 144)	*A. argentea*	55
		L. theobromae (GK-1)	*Cocos nucifera*	106
		L. pseudotheobromae (APR5)	*Andrographis paniculata*	98
		L. citricola (ALG111 and ALG39)	*C. sinensis*	84
131	2-(4-Hydroxyphenyl)acetic acid	*L. theobromae* (BPPCA 144)	*A. argentea*	55
132	3-Hydroxyphenylacetic acid	*L. citricola* (ALG111)	*C. sinensis*	84
133	4-Hydroxyphenylacetic acid	*L. citricola* (ALG111)	*C. sinensis*	84
		L. theobromae (TBRC 15112)	*A. aspera*	
134	6-Methylsalicylic acid	*L. theobromae* (PSU-M35)	*Garcinia mangostana*	108
135	Scytalone	*L. theobromae* (CAA019 and CBS339.90)	*C. nucifera*, and human	46
136	3-Hydroxybenzoic acid	*L. citricola* (ALG111)	*C. sinensis*	84
137	4-Hydroxybenzoic acid	*L. theobromae*	*Psidium guajava*	155
		L. hormozganensis (CMM0126)	*V. vinifera*	107
		L. citricola (ALG111)	*C. sinensis*	84
		Lasiodiplodia sp.	*H. impetiginosus*	103
138	3ξ-(1ξ-Hydroxyethyl)-7-hydroxy-1-isobenzofuranone	*Lasiodiplodia venezuelensis* (A02EtM)	*Astrocaryum sciophilum*	95
139	*t*-Butylhydroquinone	*L. pseudotheobromae* (APR5)	*A. paniculata*	98
140	*p*-Cresol	*L. pseudotheobromae* (APR5)	*A. paniculata*	98
141	*N*-(4-Hydroxyphenyl)acetamide	*L. theobromae* (TBRC 15112)	*A. aspera*	54
142	4-Hydroxyphenylacetamide	*Lasiodiplodia* sp.	*H. impetiginosus*	103
143	Phenylacetic acid	*L. citricola* (ALG111)	*C. sinensis*	84
144	Cinnamic acid	*L. citricola* (ALG111)	*C. sinensis*	84
145	Protocatechuic acid	*L. citricola* (ALG111)	*C. sinensis*	84
		L. theobromae	*Musa paradisiaca*	40
146	Syringic acid	*L. citricola* (ALG111)	*C. sinensis*	84
147	Vanillic acid	*L. citricola* (ALG111)	*C. sinensis*	84
148	*O*-Methyl alboatrin	*L. theobromae* (NSTRU-PN1.4)	Soil	110
149	Salicylic acid	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85

A strain of *L. citricola* (previously known as *Lasiodiplodia mitidjana*) isolated from *C. sinensis* turned out to be a good producer of phenol compounds, including protocatechuic acid, syringic acid and vanillic acid (**145–147**).[84] *Lasiodiplodia citricola* also produces phenylacetic acid (**143**), a phenyl derivative that has been shown to be an active auxin.[84] However, its effect is much weaker than the effect of indole-3-acetic acid, the other auxin produced by *Lasiodiplodia* spp.[152,153]

2.12 Preussomerins

Preussomerins are natural products having an epoxynaphthoquinone structure linked to a bi-snaphthoquinone spiroketal moiety as a common structural unit. Based on their structural features, these natural products can be divided into three subclasses: two-oxygen-bridge-type, three-oxygen-bridge-type and those with two oxygen bridges

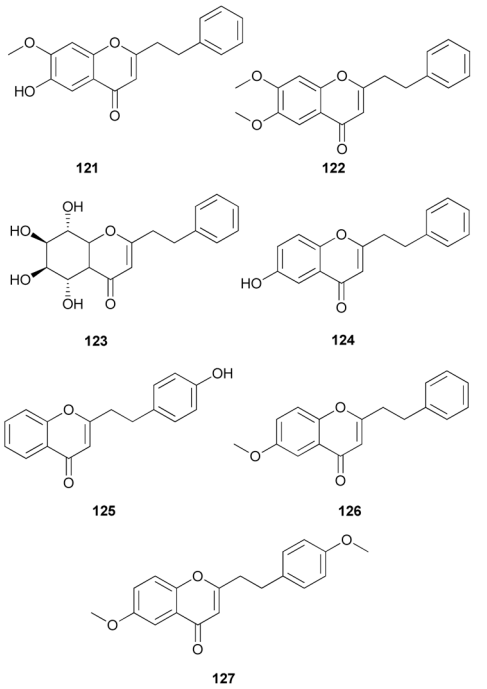

Fig. 12 Chemical structures of the 2-(2-phenylethyl)chromones.

and one C–C bridge.[156] Nine preussomerins with two oxygen bridges (**162**, **163**, and **165–171**) and fifteen preussomerins with three oxygens bridges (**150–161**, **164**, **172** and **173**) have been isolated from this fungal genus (Table 6 and Fig. 14). Most of them are well-known fungal secondary metabolites, including the first preussomerin, named preussomerin A (**152**), identified in 1990 from the coprophilous fungus *Preussia isomera*.[157] Two new preussomerins derivatives, *i.e.*, lasiodiplodiapyrones A and B (**172** and **173**, respectively), belonging to the subclass with three oxygen bridges, have been isolated from *L. pseudotheobromae*. Compared to the common preussomerins, these compounds possess an unexpected 6-methyl-4*H*-furo[3,2-*c*] pyran-4-one moiety, a highly functionalized conjoint and a complicated polycyclic ring system. These metabolites were isolated and characterized *via* spectroscopic techniques, along with two known congeners, preussomerin B (**153**) and preussomerin SA1 (**164**).[158] A novel two-oxygen-bridge-type preussomerin named mitidjospirone (**162**) was isolated and identified from the mycelial extract of *L. citricola*, together with several known compounds including palmarumycin JC1 (**163**). Mitidjospirone owes its trivial name to its fungal producer, formerly known as *L. mitidjana*.[84] Chloropreussomerins A and B (**150** and **151**, respectively) are two new chlorinated preussomerins isolated from a mangrove endophytic strain of *L. theobromae*. Other known preussomerins have been isolated from the same strain and identified as preussomerin A (**152**), preussomerin C (**154**), preussomerin D (**155**), preussomerin F (**156**), preussomerin G (**157**), preussomerin H (**158**), preussomerin K (**159**), and Ymf 1029 E (**161**).[159]

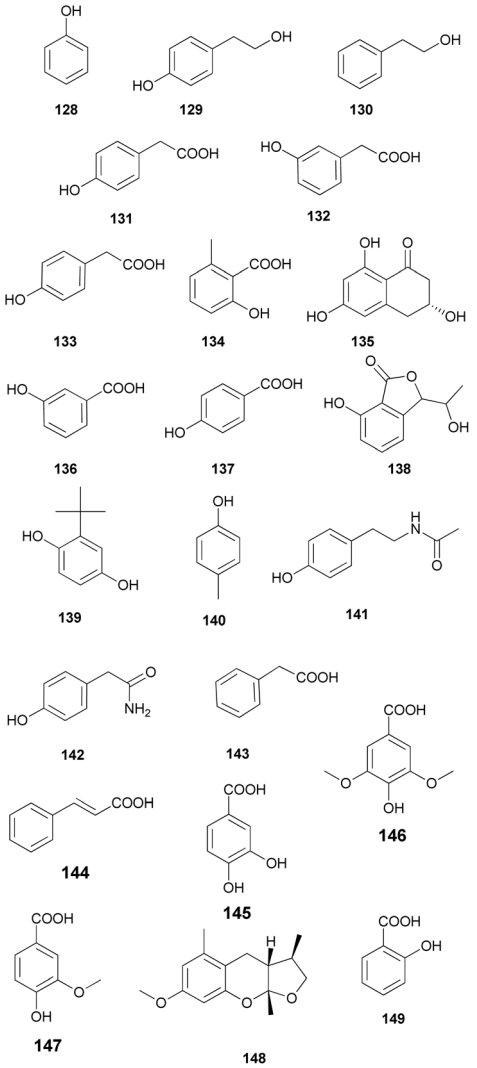

Fig. 13 Chemical structures of the phenyl and phenol derivatives.

2.13 Resorcinol and β-resorcylic acid derivatives

Resorcinol derivatives possess a 1,3-dihydroxybenzene core, which is a scaffold widespread in nature.[161–164] With the exception of 3-(2-ethoxycarbonyl-3,5-dihydroxyphenyl)propionic acid,[165] novel resorcinol derivatives have been found in cultures of *Lasiodiplodia* spp. (Table 7 and Fig. 15).[154,166]

Three novel alkylresorcinols (**174–176**) have been isolated from an endophytic strain of *Lasiodiplodia* sp. obtained from a traditional Chinese medical plant *Houttuynia cordata*. Alkylresorcinols, also known as resorcinolic lipids, are characterized by an alkyl or an alkenyl chain at 5-position of the aromatic ring linked to the 1,3-dihydroxybenzene skeleton.[161] Among the three new compounds identified, adenine alkylresorcinol (**174**) is an unusual alkylresorcinol with an adenine-alkyl resorcinol conjoined skeleton.[154]

β-Resorcylic acid derivatives are members of a unique fungal metabolites class characterized by a 12- and 14-membered macrolactone ring linked to a 2,4-dihydroxybenzoic acid residue. Since their first identification, over 200 β-resorcylic

Table 6 List of the preussomerins produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Preussomerins				
150	Chloropreussomerin A	*L. theobromae* (ZJ-HQ1)	*Acanthus ilicifolius*	159
151	Chloropreussomerin B	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
152	Preussomerin A	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
153	Preussomerin B	*L. pseudotheobromae* (414-JZ-40)	Soil	158
154	Preussomerin C	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
155	Preussomerin D	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
156	Preussomerin F	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
157	Preussomerin G	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
158	Preussomerin H	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
159	Preussomerin K	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
160	Preussomerin M	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
161	Ymf 1029 E	*L. theobromae* (ZJ-HQ1)	*A. ilicifolius*	159
162	Mitidjospirone	*L. citricola* (ALG111)	*C. sinensis*	84
163	Palmarumycin JC1	*L. citricola* (ALG111)	*C. sinensis*	84
164	Preussomerin SA1	*L. pseudotheobromae* (414-JZ-40)	Soil	158
165	(+)-(*R*)-CJ-12372	*Lasiodiplodia venezuelensis* (A02EtM)	*Astrocaryum sciophilum*	95
166	(+)-(*R*)-Palmarumycin EG1	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
167	(*R*)-4-Methoxy-3,4-dihydro-2*H*-spiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxin]-6-ol	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
168	Palmarumycin LP1	*L. pseudotheobromae* (XSZ-3)	*Camptotheca acuminata*	160
169	Ascochytatin	*L. pseudotheobromae* (XSZ-3)	*C. acuminata*	160
170	Sch 50676	*L. pseudotheobromae* (XSZ-3)	*C. acuminata*	160
171	Cladospirone B	*L. theobromae* (MJ2211)	*Vitex pinnata*	105
		L. pseudotheobromae (XSZ-3)	*C. acuminata*	160
172	Lasiodiplodiapyrone A	*L. pseudotheobromae* (414-JZ-40)	Soil	158
173	Lasiodiplodiapyrone B	*L. pseudotheobromae* (414-JZ-40)	Soil	158

acid derivatives have been reported from different genera of fungi, including *Aigialus*, C*urvularia*, *Lasiodiplodia*, *Penicillium*, and *Pochonia*.[167]

Lasiodiplodia theobromae was found to be a remarkable producer of these compounds, which are often named lasiodiplodins (Table 7 and Fig. 15). (*R*)-Lasiodiplodin (**177**) and (*R*)-de-*O*-methyllasiodiplodin (**185**) are the first members of the β-resorcylic acid derivatives class to be found in the cultural filtrate of *Lasiodiplodia* spp. A series of compounds belonging to this class of natural products has been isolated from mangrove endophytic strains of *Lasiodiplodia* spp. (Table 7).[168–171]

Among them, several novel lasiodiplodins (**180**, **181**, **183**, **185**, **190**, **192**, **195**, **197**, **199–201**, **204**, and **205**) have been identified from *Lasiodiplodia* sp. 318[#] isolated from *Excoecaria agallocha*.[168,169]

A mangrove endophytic strain of *L. theobromae* produced an unprecedented β-resorcylic acid derivative named lasiodiplactone A (**196**) possessing a pyran ring and a furan ring.[170]

A strain of *L. theobromae* isolated from the inner tissue of a dead branch of the mangrove plant *Xylocarpus granatum* produced ten β-resorcylic acid derivatives, including five lasiodiplodins, in which their macrocyclic ring is affected by modifications that cause the opening of the ring and diverse substituents in the *ortho* to the carboxylic group (*i.e.* hydroxyheptyl or hydroxynonyl moieties).[171]

Due to their abundant production by *Lasiodiplodia* spp., the employment of these compounds for fungal chemotaxonomy has been proposed.[92] In fact, secondary metabolites could be very useful chemotaxonomic markers and have already been used successfully in large genera such as *Alternaria*, *Aspergillus*, *Fusarium*, *Penicillium*, and *Xylaria*.[172] In this respect, the exclusive production of lasiodiplodins by the unidentified endophytic fungus ZZF3 suggested that this isolate possibly belongs to the *Lasiodiplodia* genus,[173] which is why this strain is included in the present review.

2.14 Terpenoids

Terpenoids are the most abundant and structurally diverse plant secondary metabolites derived from a five-carbon isoprene unit.[183–185] Steroids are complex four-ring organic compounds obtained from terpenoid precursors, which play many roles and functions in microorganisms and organisms.[186,187] The well-known sterols ergosterol, ergosterol peroxide and stigmasterol (**217–219**, respectively) have been isolated from the endophytic fungus *L. theobromae* derived from the root of *Aglaia argentea* (Table 8).[188] Although this is the first report on the isolation of these steroids from species of *Lasiodiplodia*, this detection is not surprising because ergosterol represents the most abundant sterol in fungal cell membranes and it is critical for defining membrane fluidity and regulating cellular processes.[189]

Eight new ergostene-type steroids (**220–223** and **225–228**), along with a known congener (**224**), have been isolated and identified as products of *L. pseudotheobromae* from the soil of Hainan wetland park. Their structures have been elucidated

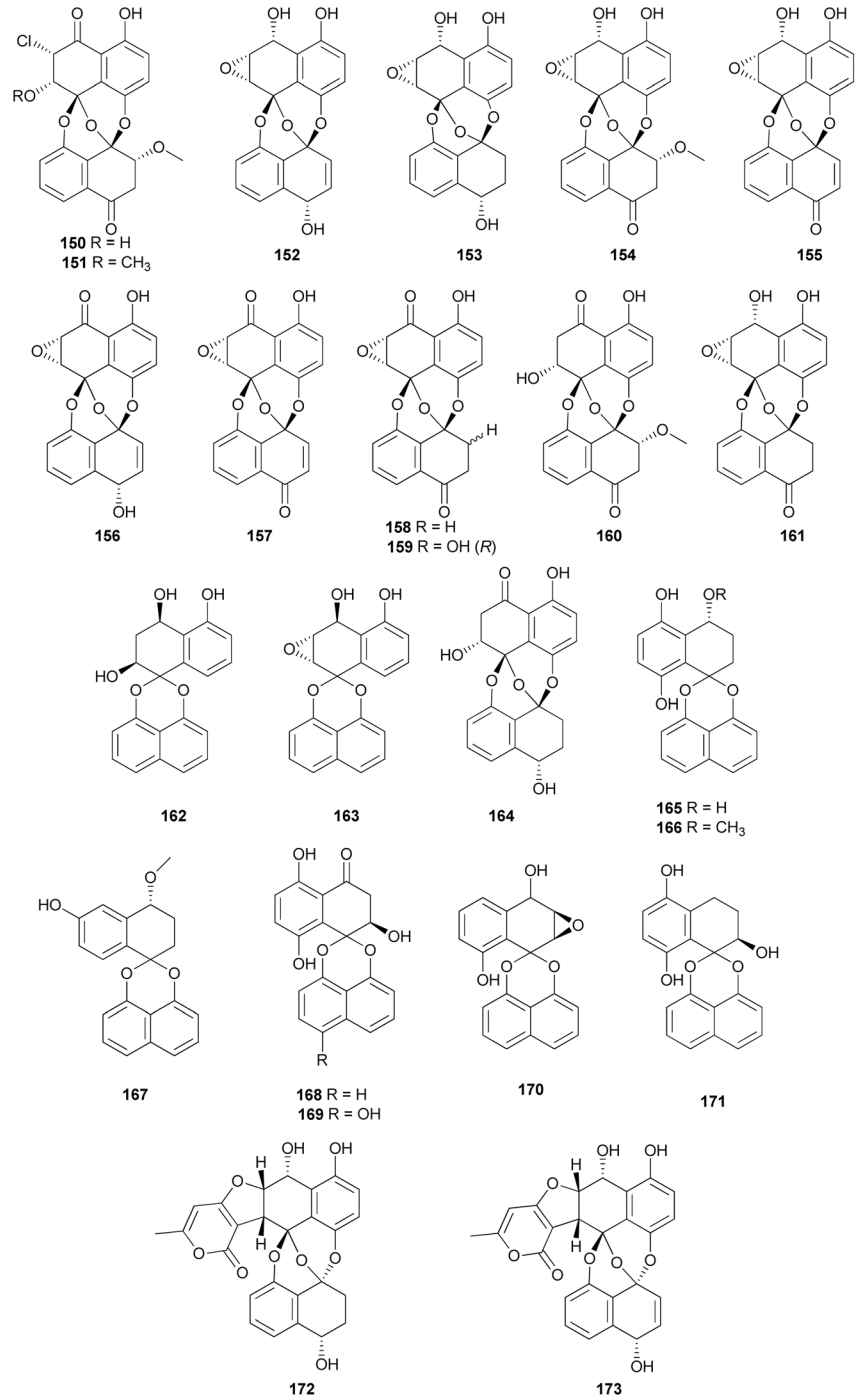

Fig. 14 Chemical structures of the preussomerins.

based on spectroscopic methods and single crystal X-ray diffraction analysis (Table 8 and Fig. 16).[158,190,191]

HPLC-ESI-MS/MS investigations of the metabolite profiles of *L. theobromae* strains, isolated from Cuban *Citrus cinensis* and from the wood of Brazilian Amazonia,[85] revealed two other phytohormones belonging to the class of terpenoids: gibberellic acid and abscisic acid (**230** and **231**, respectively). These compounds are commonly produced by plants, influencing their growth and development, but are quite rare as fungal products.[192] Several phytohormones have been simultaneously identified in the fermentation broth of strains of *Lasiodiplodia* spp. Some of them (*e.g.*, indole acetic acid, jasmonic acid and its amino acid conjugates) have been discussed in the sections dedicated to jasmonates and indoles. Little is known about their role and importance beyond plant systems. Plant-associated fungi appear to be more likely to produce phytohormones to alter their flow in host plants.[193] The detection of some phytohormones in cultures of *L. theobromae*[85] and *L. iranensis*[42] supports this view considering that these strains were isolated from plants.

Table 7 List of the resorcinol and β-resorcylic acid derivatives produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Resorcinol and β-resorcylic acid derivatives				
174	Adeninealkylresorcinol	*Lasiodiplodia* sp.	*Handroanthus impetiginosus*	154
175	3-*O*-Methyl-5-(8-methoxyl-6-oxononyl)-resorcinol	*Lasiodiplodia* sp.	*H. impetiginosus*	154
176	3-*O*-Methyl-5-[(7*E*)-6-oxo-7-nonenyl]-resorcinol	*Lasiodiplodia* sp.	*H. impetiginosus*	154
177	(*R*)-Lasiodiplodin	*Lasiodiplodia theobromae* (IFO 31059)	—	174 and 175
		L. theobromae	—	100
		L. theobromae (CSS01s)	*V. vinifera*	102
		L. pseudotheobromae (J-10)	*Sarcandra glabra*	176
		L. theobromae (CAA019)	*C. nucifera*	46
		Lasiodiplodia sp. (318[#])	*Excoecaria agallocha*	168 and 169
		L. citricola (ALG111 and ALG39)	*C. sinensis*	84
178	(*S*)-Lasiodiplodin	*L. theobromae* (PSU-M35)	*Garcinia mangostana*	108
		L. theobromae (TBRC 15112)	*Achyranthes aspera*	54
179	(3*R*,4*S*)-4-Hydroxy-lasiodiplodin	*L. theobromae* (IFO 31059)	—	177
180	(3*R*,5*R*)-5-Hydroxy-lasiodiplodin	*L. theobromae* (IFO 31059)	—	177
		L. mediterranea (B6)	*V. vinifera*	131
		L. theobromae	*S. tuberosum*	178
		L. theobromae (PSU-M35)	*G. mangostana*	108
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169
181	(3*R*,5*S*)-5-Hydroxy-lasiodiplodin	*L. theobromae* (IFO 31059)	—	174, 175, 177 and 178
		L. theobromae (PSU-M35)	*G. mangostana*	108
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169
182	(3*R*,6*S*)-6-Hydroxy-lasiodiplodin	*L. theobromae* (Shimokita 2)	*M. indica*	179
183	(12*E*,15*R*)-5-Hydroxy-3-methoxy-16-methyl-8,9,10,11,14,15-hexahydro-1*H*-benzo[*c*][1]oxacyclodocecin-1-one	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
184	Botryosphaeriodiplodin	*L. mediterranea* (B6)	*V. vinifera*	131
		L. theobromae (PSU-M35)	*G. mangostana*	108
185	(3*R*)-De-*O*-methyl-lasiodiplodin	*L. theobromae*	*Pyrenula bahiana*	180
		L. theobromae (3PR3)	*Mapania kurzii*	181
		L. theobromae	—	100
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169
		L. theobromae (MJ2211)	*Vitex pinnata*	105
		L. theobromae (M4.2-2)	*Mangrove* sediment	57
186	4-Hydroxy-de-*O*-methyl-lasiodiplodin	*L. theobromae* (3PR3)	*M. kurzii*	181
187	(3*R*,5*R*)-5-Hydroxy-de-*O*-methyllasiodiplodin	*L. theobromae*	—	177
188	(6*R*)-6-Hydroxy-de-*O*-methyllasiodiplodin	*L. theobromae* (3PR3)	*M. kurzii*	181
		L. theobromae (IFO 31059)	—	177
189	5-Oxo-lasiodiplodin	*L. theobromae* (IFO 31059)	—	177 and 178
190	(3*R*)-7-Oxo-lasiodiplodin	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
191	(3*S*)-7-Oxo-de-*O*-methyllasiodiplodin	*L. theobromae* (GI-1005)	*Rhizophora mucronata*	165
192	(3*R*,5*E*)-5-Etheno-lasiodiplodin	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
193	(3*S*,7*R*)-9-Etheno-7-hydroxy-13-*O*-methyl-de-*O*-methyllasiodiplodin	*L. theobromae* (GI-1005)	*R. mucronata*	165
194	(*E*)-9-Etheno-de-*O*-methyl-lasiodiplodin	*L. theobromae* (3PR3)	*M. kurzii*	181
195	(*R*)-14-Methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1*H*-benzo[*c*][1]oxacyclododecine-1,11,12-trione	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
196	Lasiodiplactone A	*L. theobromae* (ZJ-HQ1)	*Acanthus ilicifolius*	170
197	*epi*-8,9-Dihydrogreensporone C	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
198	(−)-(*R*)-Nordinone	*L. theobromae* (M4.2-2)	Mangrove sediment	57
199	(*R*)-Zearalenone	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
200	2,4-Dihydroxy-6-nonylbenzoate	*Lasiodiplodia* sp. (318[#])	*E. agallocha*	168 and 169
201	Ethyl (*S*)-2,4-dihydroxy-6-(8-hydroxynonyl)benzoate	*L. theobromae* (GI-1005)	*R. mucronata*	165
		L. theobromae (GC-22)	*Xylocarpus granatum*	171
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169
202	Ethyl 2,4-dihydroxy-6-(8-hydroxyheptyl)benzoate	*L. theobromae* (GI-1005)	*R. mucronata*	165
		L. theobromae (GC-22)	*X. granatum*	171
203	Ethyl 2,4-dihydroxy-6-(4-methoxycarbonylbutyl)benzoate	*L. theobromae* (GC-22)	*X. granatum*	171
204	Isobutyl (*S*)-2,4-dihydroxy-6-(8-hydroxynonyl)benzoate	*L. theobromae* (GC-22)	*X. granatum*	171
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169

Table 7 (*Contd.*)

No.	Compound	Fungal producer (strain)	Source	Ref.
205	Ethyl 2,4-dihydroxy-6-(8-oxononyl)benzoate	*L. theobromae* (GI-1005)	*R. mucronata*	165
		Lasiodiplodia sp. (318[#])	*E. agallocha*	168 and 169
		L. theobromae (GC-22)	*X. granatum*	171
206	(3*S*,7*R*)-7-Hydroxy-13-*O*-methyl-de-*O*-methyllasiodiplodin	*L. theobromae* (GI-1005)	*R. mucronata*	165
207	(15*S*)-De-*O*-methyllasiodiplodin	*L. theobromae* (GC-22)	*X. granatum*	171
		L. brasiliensis (WS-TS-A1)	*Cannabis sativa*	182
208	(13*S*,15*S*)-13-Hydroxy-de-*O*-methyllasiodiplodin	*L. theobromae* (GC-22)	*X. granatum*	171
209	(14*S*,15*S*)-14-Hydroxy-de-*O*-methyllasiodiplodin	*L. theobromae* (GC-22)	*X. granatum*	171
210	(13*R*,14*S*,15*S*)-13,14-Dihydroxy-de-*O*-methyllasiodiplodin	*L. theobromae* (GC-22)	*X. granatum*	171
211	(*E*)-9-Etheno-de-*O*-methyl-lasiodiplodin	*L. theobromae* (3PR3)	*M. kurzii*	181
212	6-Oxo-de-*O*-methyl-lasiodiplodin	*L. theobromae* (3PR3)	*M. kurzii*	181
213	Ethyl (6′*R*)-2,4-hydroxy-6-(6′-hydroxyheptyl)-benzoate	*L. theobromae* (IFO 31059)	—	166
214	Isobutyl (6′*R*)-2,4-hydroxy-6-(6′-hydroxyheptyl)-benzoate	*L. theobromae* (IFO 31059)	—	166
215	3-(2-Ethoxycarbonyl-3,5-dihydroxyphenyl)propionic acid	*L. theobromae* (GC-22)	*X. granatum*	171
		L. theobromae (GI-1005)	*R. mucronata*	165
216	(3*S*)-3-[(*R*)-8-Hydroxynonyl]-6-hydroxy-8-methoxy-3,4-dihydroisochroman-1-one	*Lasiodiplodia* sp.	*H. impetiginosus*	154

2.15 Miscellaneous

This category includes products of *Lasiodiplodia* spp. that have no structural affinity with previous classes. As can be seen in Table 8 and Fig. 17, the members of this group present heterogenous structures ranging from simple compounds, *e.g.*, glycerol (**232**) and 2,3-butanediol (**269**), to very complex products, *e.g.* colletopeptide B (**234**) and taxol (**235**). Some compounds listed in this section (*i.e.*, glycerol, succinic acid, and uracil) are primary metabolites and, for this reason, are commonly found in natural sources. However, Table 8 presents metabolites exclusively produced by *Lasiodiplodia* spp. This is the case of a new dihydronaphthalene-2,6-dione derivative named botryosphaeridione, which is produced by strains of *L. theobromae*.[108,110]

3 Biological activities of *Lasiodiplodia* spp. secondary metabolites

Secondary metabolites are important mediators of biological interactions and represent promising sources of drugs. Given their relevance in many fields of research, the biological properties of secondary metabolites have been investigated in most papers on the metabolism of *Lasiodiplodia* spp. (Table S1).

Since some of these compounds are well-known from various natural sources and have been extensively studied in dedicated articles, the present section focuses exclusively on bioactivities documented for metabolites isolated from *Lasiodiplodia* spp., including antimicrobial, cytotoxic, immunomodulatory, phytotoxic (Fig. 18).

Several *Lasiodiplodia* spp. are associated with plant diseases, with the possible involvement of toxic secondary metabolites in various symptoms. In fact, the association of *Lasiodiplodia* spp. with economically and ecologically important plants has encouraged researchers to conduct phytotoxicity tests on fungal metabolites to better understand their role in symptom expression. Experimental data (Table S1) from phytotoxicity assays have confirmed that some secondary metabolites produced by pathogenic strains of *Lasiodiplodia* spp. can be considered phytotoxins harmful to plants even at low concentrations and may be involved in the infection mechanisms. For instance, *Lasiodiplodia* spp. are known pathogens of grapevine, causing aggressive diseases, such as canker and dieback, which symptoms, particularly the foliar ones, can be attributed to the fungal production of toxic secondary metabolites.[101,200] In fact, metabolites (*i.e.*, (−)-jasmonic acid (**65**), nigrosphaerilactone (**94**), lasiolactols A and B (**102** and **103**, respectively), and botryosphaeriodiplodin (**184**)) from a grapevine strain of *L. mediterranea* showed moderate activity in tests conducted on grapevine cv. Inzolia leaves (Table S1). The phytotoxicity of these compounds increased with increasing concentrations; moreover, **65** was the most active compound (biggest necrotic spots on detached grapevine leaves).[131] However, some metabolites exert phytotoxic effects not exclusively on their hosts but also on a wide range of plants. This is exemplified by (−)-mellein (**58**), which exhibits toxicity toward several plants, including *Bromus* sp., *Cynodon dactylon*, *Loietto perenne*, *Setaria italica* and members of the *Valerianaceae* family (Table S1). When tested with a leaf puncture assay on its host plant (*Tridax procumbus*), (−)-mellein induced necrotic circular lesions within 2 days, closely resembling those caused by the pathogen (*L. pseudotheobromae*). In contrast, assays on cultivated species showed no effect on *Solanaceous* species (red pepper and potato), Cucurbitaceae (melon and cucumber), and Leguminosae (cowpea), whereas severe necrosis was observed on monocotyledon Poaceae weeds. These results indicated that (−)-mellein exhibits selective bioherbicidal activity, with a stronger impact on monocotyledons than dicotyledons.[109] Another important phytotoxic metabolite of *Lasiodiplodia* spp. is (−)-jasmonic acid (**65**), which demonstrated significant phytotoxicity against several plants (Table S1). In particular, this phytotoxin induced

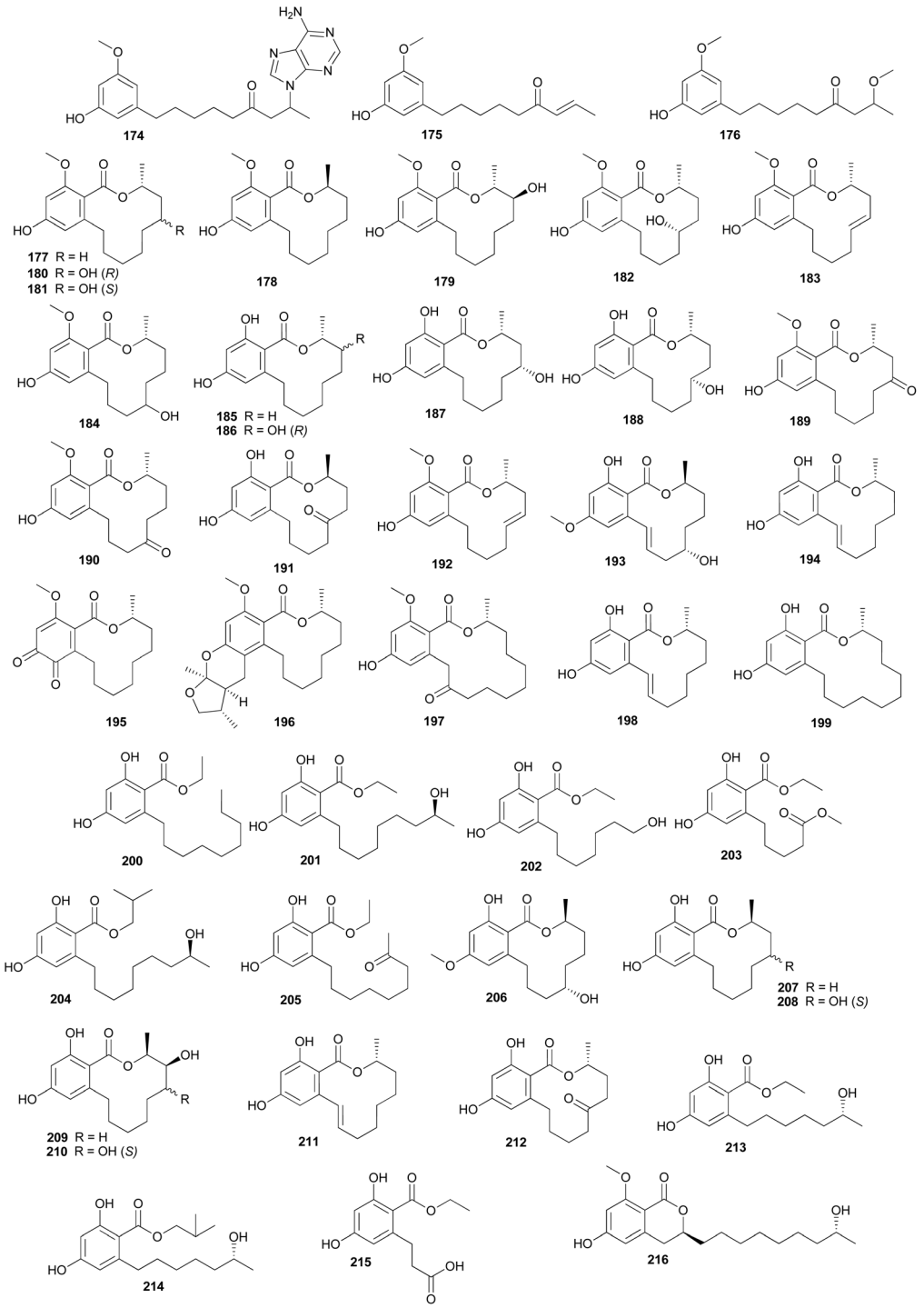

Fig. 15 Chemical structures of the resorcinol and β-resorcylic acid derivatives.

the development of brown necrotic lesions on leaves of *Rosa* sp.,[132] *Quercus suber*,[129] *Vitis vinifera*[129] and *Solanum lycopersicum*.[46] As reported in Section 2.8, (−)-jasmonic acid is primarily a phytohormone and its fungal production could be important to manipulate the host physiology for survival, colonization, and nutrient acquisition. In addition to (−)-jasmonic acid, *Lasiodiplodia* spp. produce other compounds well-known as phytohormones, *e.g.*, salicylic acid (**149**), gibberellic acid (**230**) and abscisic acid (**231**). Therefore, phytotoxic metabolites are not the only compounds that might be involved in the dynamic plant–fungus interactions. In fact, it was also observed that several fatty acid esters produced by *L. theobromae* showed an effect of plant growth regulation in the model plant *Nicotiana tabacum*.[81,82] In addition, theobroxide (**1**), its related compounds (**4–6**) and some β-resorcylic acid derivatives (**179–182**) demonstrated the ability to induce micro-tuber formation in potatoes

Table 8 List of the terpenoids and miscellaneous compounds produced by *Lasiodiplodia* spp.

No.	Compound	Fungal producer (strain)	Source	Ref.
Terpenoids				
217	Ergosterol	*Lasiodiplodia theobromae* (#009)	*Psidium guajava*	111
		L. theobromae (Arg-8)	*Aglaia argentea*	188
218	Ergosterol peroxide	*L. theobromae* (Arg-8)	*A. argentea*	188
219	Stigmasterol	*L. theobromae* (Arg-8)	*A. argentea*	188
220	(22*E*,24*R*)-4α,5α-Epoxyergosta-9α,14β-dihydroxy-7,22-diene-3,6-dione	*Lasiodiplodia pseudotheobromae* (414-JZ-40)	Soil	158
221	(22*E*,24*R*)-4α,5α-Epoxyergosta-9α,14α-dihydroxy-7,22-diene-3,6-dione	*L. pseudotheobromae* (414-JZ-40)	Soil	158
222	12α-Hydroxyergosta-7,22,24(28)-triene-3-one	*L. pseudotheobromae* (414-JZ-40)	Soil	158
223	3β,12α-Dihydroxyergosta-7,24(28)-diene	*L. pseudotheobromae* (414-JZ-40)	Soil	158
224	(22*E*,24*R*)-9α,14β-Dihydroxyergosta-4,7,22-triene-3,6-dione	*L. pseudotheobromae* (414-JZ-40)	Soil	158
225	3β,14β-Dihydroxy-6-oxo-A-nor-ergosta-7,22-diene-4-oic acid δ-lactone	*L. pseudotheobromae* (414-LY-1)	Soil	190 and 191
226	2β,3β,12α-Trihydroxyergosta-7,22-diene	*L. pseudotheobromae* (414-LY-1)	Soil	190 and 191
227	2β,3β,12α-Trihydroxyergosta-7,24(28)-diene	*L. pseudotheobromae* (414-LY-1)	Soil	190 and 191
228	9α,11α,15α-Trihydroxyergosta-4,6,8(14),22-tetraen-3-one	*L. pseudotheobromae* (414-LY-1)	Soil	190 and 191
229	Cholestanol glucoside	*L. theobromae*	*Saraca asoca*	194 and 195
230	Gibberellic acid (GA3)	*Lasiodiplodia theobromae* (2334, 1517 and 83)	*Citrus cinensis* and wood	85
231	Abscisic acid	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
		Lasiodiplodia iranensis (F0619)	*Avicennia germinans*	42
Miscellaneous				
232	Glycerol	*Lasiodiplodia citricola* (ALG11, ALG39 and ALG81)	*Citrus sinensis*	84
		Lasiodiplodia avicenniae (P2P4)	*Avicennia alba*	196
233	Eugenol	*L. citricola* (ALG11)	*C. sinensis*	84
234	Colletopeptide B	*L. theobromae* (BPPCA 144)	*A. argentea*	55
235	Taxol	*L. theobromae*	*Morinda citrifolia*	197 and 198
		L. theobromae (BT 115)	*Taxus baccata*	199
236	2,4,6-Trimethyloct-2-enoic acid, 1,2,6,8a-tetrahydro-7-hydroxy-1,8a-dimethyl-6-oxo-2-naphtalenyl ester	*L. theobromae* (#009)	*Psidium guajava*	111
237	Aranorosinol B	*L. theobromae*	*P. guajava*	155
238	Lasiodiplin	*L. theobromae* (TBRC 15112)	*Achyranthes aspera*	54
239	5-Hydroxymethyl-2-furancarboxylic acid	*Lasiodiplodia venezuelensis*	*Astrocaryum sciophilum*	94
240	(*Z*)-3-((2*R*,3*R*,6*R*)-3-Hydroxy-6-((*R*)-1-hydroxyethyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylamide	*L. venezuelensis*	*A. sciophilum*	94
241	(2*Z*,4*Z*,8*E*)-6,7-Dihydroxydeca-2,4,8-trienoic acid	*L. venezuelensis*	*A. sciophilum*	94
242	Uridine	*L. venezuelensis*	*A. sciophilum*	94
243	Norharman	*L. theobromae* (AUMC 8903)	*Dracaena draco*	43
244	Bergapten	*L. theobromae* (AUMC 8903)	*D. draco*	43
245	Meranzin	*L. theobromae* (AUMC 8903)	*D. draco*	43
246	Formyl indanone	*L. theobromae* (AUMC 8903)	*D. draco*	43
247	Halaminol A	*L. theobromae* (AUMC 8903)	*D. draco*	43
248	Palmitoleamide	*L. theobromae* (AUMC 8903)	*D. draco*	43
249	Palmitic amide	*L. theobromae* (AUMC 8903)	*D. draco*	43
250	Capsi amide	*L. theobromae* (AUMC 8903)	*D. draco*	43
251	Lasiodione B	*Lasiodiplodia* sp. (AD-2102)	*Artemisia desertorum*	139
252	Lasdiploic acid	*L. pseudotheobromae* (#1048AMSTYEL)	*Aegle marmelos*	137
253	Botryosphaeridione	*L. theobromae* (PSU-M35)	*Garcinia mangostana*	108
		L. theobromae (NSTRU-PN1.4)	Soil	110
254	Botryosphaerihydrofuran	*L. theobromae* (PSU-M35)	*G. mangostana*	108
255	Botryosphaerinone	*L. theobromae* (PSU-M35)	*G. mangostana*	108
256	Succinic acid	*L. theobromae* (LA-SOL3 and LA-SV1)	*Vitis vinifera*	45
		L. citricola (ALG111 and ALG81)	*C. sinensis*	84
257	(*Z*)-3-((2*R*,3*R*,6*R*)-3-Hydroxy-6-((*R*)-1-hydroxyethyl)-3,6-dihydro-2*H*-pyran-2-yl)acrylamide	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
258	Aconitate B	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
259	(3*R*,4*R*,*Z*)-4-Hydroxy-1-((2*S*,3*S*)-3-hydroxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)pent-1-en-3-yl acetate	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95

Table 8 (*Contd.*)

No.	Compound	Fungal producer (strain)	Source	Ref.
260	(2*Z*,6*Z*)-4,5,8,9-Tetrahydroxydeca-2,6-dienamide	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
261	(2*Z*,4*Z*,8*E*)-6,7-Dihydroxydeca-2,4,8-trienoic acid	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
262	(2*R*)-Butylitaconic acid	*L. venezuelensis* (A02EtM)	*A. sciophilum*	95
263	Erythritol	*L. pseudotheobromae* (APR5)	*Andrographis paniculata*	98
264	Niacin	*L. pseudotheobromae* (APR5)	*A. paniculata*	98
265	Uracil	*L. theobromae* (TBRC 15112)	*A. aspera*	54
266	1,8-Dihydroxyantraquinone	*L. citricola* (ALG111)	*C. sinensis*	84
267	Vitamin B6 (pyridoxine)	*L. citricola* (ALG111, ALG39, ALG81 and ALG34)	*C. sinensis*	84
268	1,3-Butanediol	*L. avicenniae* (P2P4)	*A. alba*	196
269	2,3-Butanediol	*L. avicenniae* (P2P4)	*A. alba*	196
270	4,5,6-Trimethyl-2(1*H*)-pyrimidinone	*L. theobromae* (NSTRU-PN1.4)	Soil	110
271	L-Isoleucinamide	*L. theobromae* (NSTRU-PN1.4)	Soil	110
272	Zeatin	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85
273	Zeatin riboside	*L. theobromae* (2334, 1517 and 83)	*C. cinensis* and wood	85

(Table S1).[29,31] These results proved that compounds produced by *Lasiodiplodia* spp. could mimic or interact with plant metabolites influencing developmental processes.

In recent years, research has focused on climate change, observing that the phytotoxin-induced pathogenicity of *Lasiodiplodia* spp. responds to environmental shifts altering the microbial pathogen–host interactions. The adaptability of these

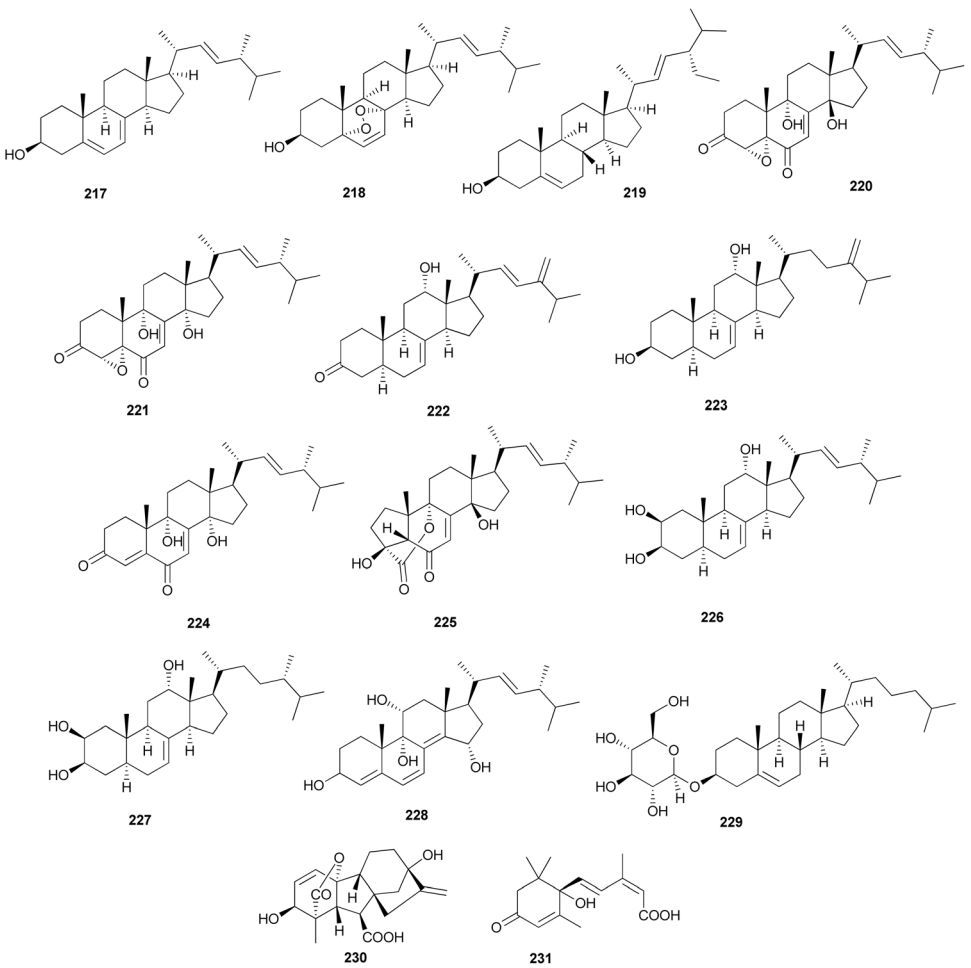

Fig. 16 Chemical structures of the terpenoids.

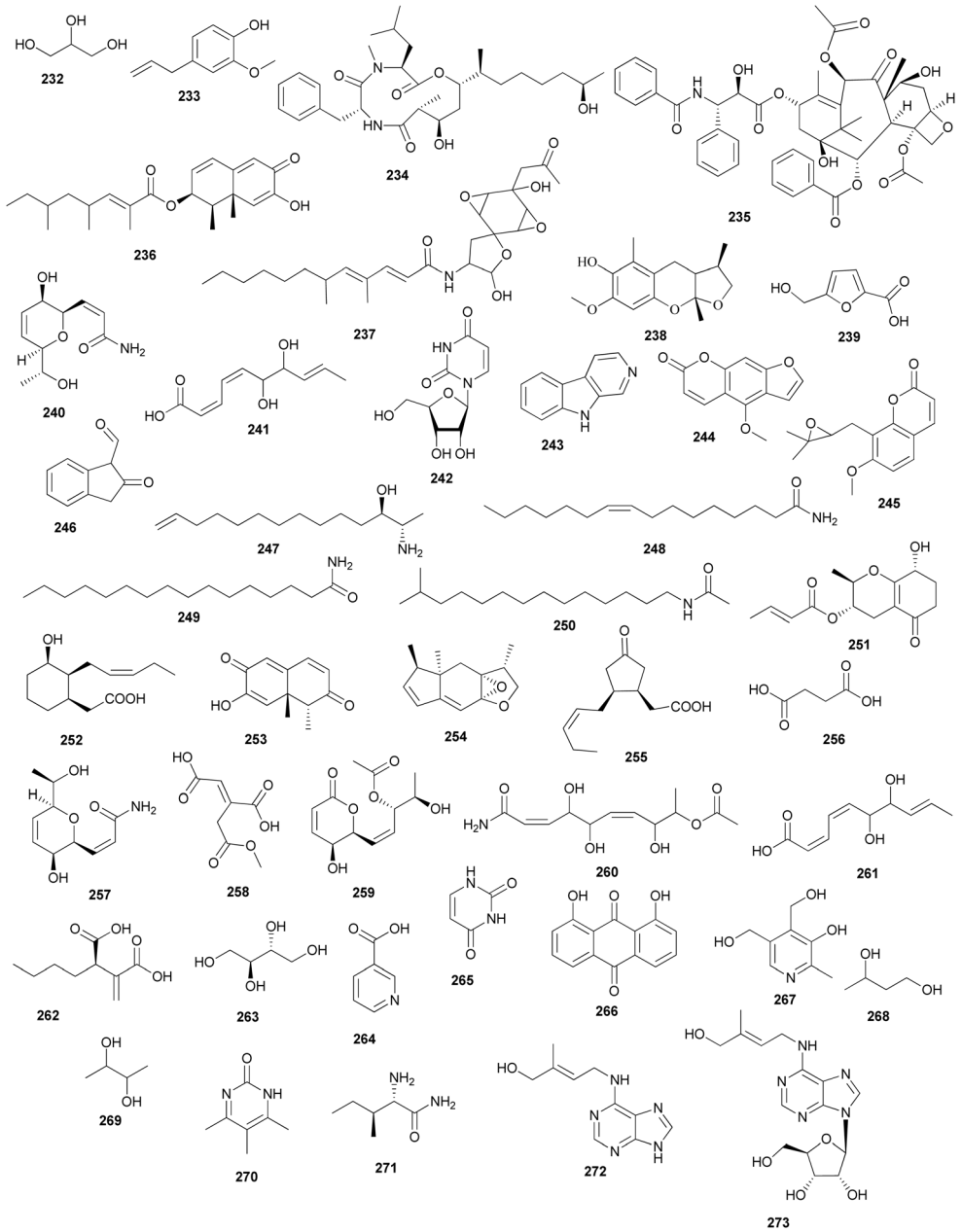

Fig. 17 Chemical structures of the miscellaneous compounds.

pathogens to new environmental conditions has raised concerns in view of a possible dramatic scenario characterized by new host colonization.[16] In fact, it was reported that higher temperatures and drought conditions are factors that promote the expansion of the host range and intensify the threat to agriculture and forestry.[5,45,46,101,201] We should not forget that *Lasiodiplodia* spp., especially *L. theobromae*, are recognized as opportunistic human pathogens. Consequently, the expansion of the host range and the increasing severity of infections pose a critical cross-kingdom risk to global health.

The adaptability of *Lasiodiplodia* spp. to their hosts is linked to the capacity to produce various metabolites under differing environmental conditions. Although the previously described phytotoxicity of these compounds undoubtedly plays a primary role during plant infection, the broad host range suggests that further bioactivities of *Lasiodiplodia* spp. metabolites should also be considered because these are not simple by-products, but tools employed as a key adaptive strategy. Indeed, the antimicrobial activity of *Lasiodiplodia* spp. secondary metabolites is particularly important for host adaptability because the fungus can use these compounds as weapons to compete with other microorganisms during host infection. Table S1 shows that several secondary metabolites have been evaluated for their antimicrobial effects. Among them, (−)-mellein (**58**) and (−)-botryodiplodin (**89**) exhibit valuable antimicrobial activities, highlighting their potential as

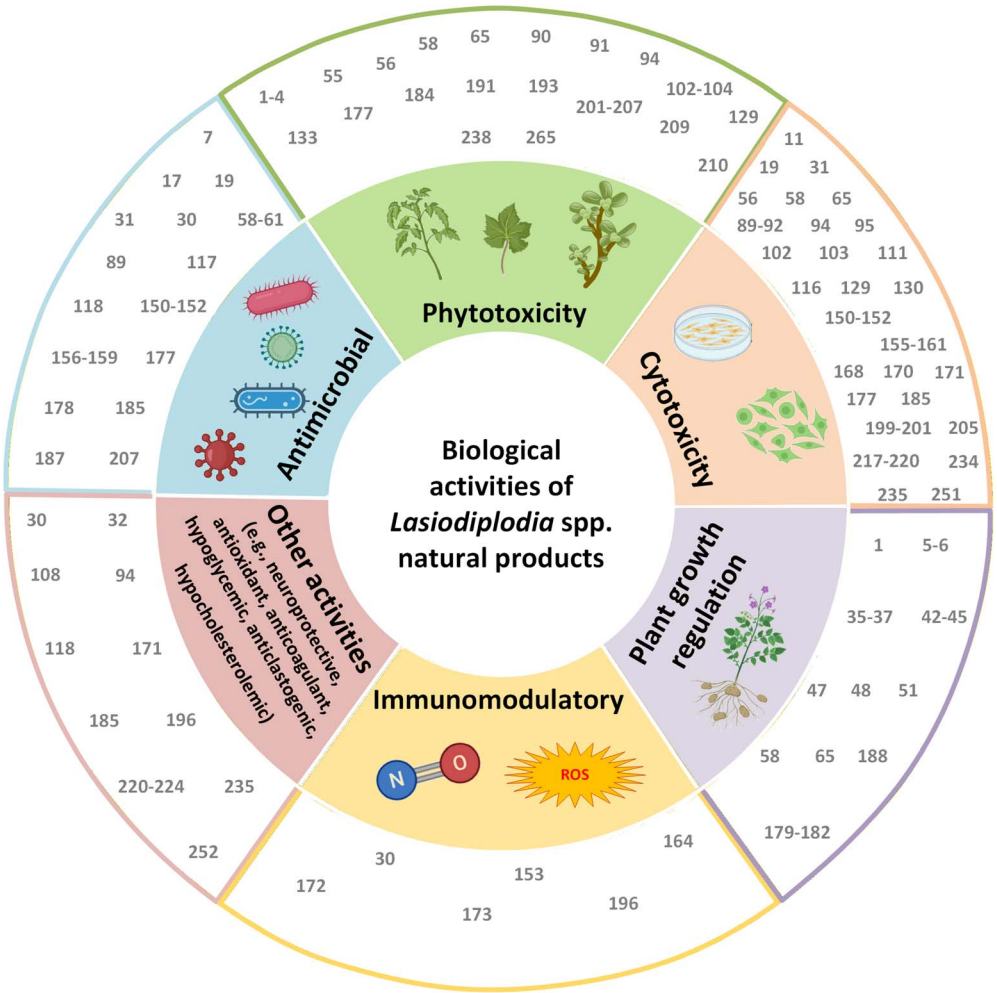

Fig. 18 Main bioactivities of the *Lasiodiplodia* spp. natural products. Metabolites in this figure are indicated by numerical codes.

bioactive lead compounds.[20,93] (−)-Mellein produced by *L. theobromae* isolated from the medicinal plant *Syzygium cumini* showed potent anti-*Xanthomonas* activity, with MIC values ranging from 1.9 to 62.5 μg mL^{-1} against 11 *Xanthomonas* strains, along with broad-spectrum antibacterial and antifungal effects with the MIC of 7.8–31.25 μg mL^{-1} and 1.9–31.25 μg mL^{-1}, respectively (Table S1). Molecular docking studies further supported its activity, revealing favourable binding interactions with proteins involved in *Xanthomonas* sp. pathogenicity. In addition, *in silico* absorption, distribution, metabolism, and excretion (ADME) studies indicated that this 3,4-dihydroisocoumarin possesses suitable oral bioavailability, balanced lipophilicity, good water solubility, favourable pharmacokinetics and overall drug-likeness profiles. (−)-Mellein complies with Lipinski's rule of five with zero violations and shows high predicted gastrointestinal absorption and blood–brain barrier permeation properties. Thus, from a medicinal chemistry perspective, no structural alerts were detected, reinforcing the potential of (−)-mellein as a promising drug candidate.[93] Even (−)-botryodiplodin displayed broad-spectrum antimicrobial properties, with well-documented inhibitory effects against both fungi and bacteria (Table S1). Therefore, its hemiacetalic γ-lactone core represents a promising scaffold for future drug discovery.[20]

The ecological success of *Lasiodiplodia* spp. could be also related to the cytotoxic and immunomodulatory activities of secondary metabolites. Some preussomerins (**150–152**, **155–161**, **164**, **168**, and **170**) displayed cytotoxicity against human cell lines. Chlorinated preussomerins (**150** and **151**) showed potent cytotoxicity against A549 and MCF-7 human cancer cell lines, with IC_{50} values ranging from 5.9 to 8.9 μM.[159] Furthermore, some preussomerins (**150–152** and **156–159**) that showed cytotoxicity were also active in antimicrobial assays against *Staphylococcus aureus* and *Bacillus subtilis*,[159] while other preussomerins (**153**, **164**, **172**, and **173**) showed suppressive effects on the production of NO.

The biological activity data reported in Table S1 highlight the dual role of *Lasiodiplodia* spp. metabolites, where they are responsible for fungal fitness and niche adaptation, but they also represent promising compounds for innovation in the agricultural, pharmaceutical, and biotechnological fields. In this respect, in addition to *in vitro* assays, reports describe some interesting *in vivo* bioactivities of exopolysaccharides produced by *L. theobromae* (Table S1). The effects of botryosphaeran (**32**)

have been investigated in streptozotocin-induced diabetic rats and in high-fat diet-fed hyperlipidemic Wistar rats, observing that this exopolysaccharide possess hypoglycaemic and hypocholesterolemic properties in conditions of diabetes mellitus and hyperlipidaemia, respectively, and may be used as an oral anti-diabetic agent.[71] Miranda *et al.*[70] evaluated the *in vivo* genotoxic activity of botryosphaeran and its effect on the clastogenicity induced by cyclophosphamide in mice using the micronucleus test in bone marrow and peripheral blood cells. Data showed that this exopolysaccharide has a protective effect of cyclophosphamide-induced clastogenicity in mice. Furthermore, an interesting study showed that when sulfonated, botryosphaeran induces anticoagulant activity in activated partial thromboplastin time and thrombin time tests, while botryosphaeran did not inhibit any of the coagulation tests. Hence, the derivatization of botryosphaeran enhanced its biological activity.[72]

4 Structure–activity relationship (SAR)

The exploration of structure–activity relationships (SARs) is supported by the idea that specific structural components represent requirements for biological activities. Although *Lasiodiplodia* spp. produce structurally diverse natural products, only a limited number of metabolites has been investigated through systematic biological screening suitable for SAR analysis. As a result, significant gaps remain in the literature, limiting a comprehensive SAR interpretation and obscuring the effect of minor structural modifications on the biological activity.

Nevertheless, several targeted studies have provided SAR insights, which are summarized below to illustrate the current state of knowledge.

As mentioned, (−)-jasmonic acid (**65**) is the parent compound of a large family of natural compounds named jasmonates (Fig. 10). (−)-Jasmonic acid is known for its role in plant growth and it is often conjugated to amino acids, particularly with isoleucine. Jasmonic acid–isoleucine has been also found as product of *L. theobromae*[85] and previous studies reported that this compound is the most biologically active plant jasmonate.[127] Three new jasmonic acid conjugates, named lasiojasmonates A–C, have been isolated from *Lasiodiplodia* sp., along with (−)-jasmonic acid and other known compounds. These compounds have been tested for phytotoxicity in a leaf-puncture assay on cork oak and grapevine leaves and on a tomato cutting assay. Interestingly, in these bioassays, only (−)-jasmonic acid caused vein necrosis or plant withering, suggesting that esterification with the lactone/lactol moiety affected the phytotoxic activity.[129] However, because only few jasmonates have been screened, the contribution of side chain substitutions, stereochemical configurations or chain length variations remains unexplored.

A remarkable evaluation of the relationships between structure and bioactivity was conducted on a series of β-resorcylic acid derivatives (Fig. 15) isolated from *Lasiodiplodia* spp. 318[#], which were tested for their cytotoxic activity against THP-1, MDA-MB-435, A549, HepG2 and HCT-116 cell lines. Among the isolated compounds, only ethyl (*S*)-2,4-dihydroxy-6-(8-hydroxynonyl)benzoate (**201**), an open-ring lasiodiplodin, showed moderate cytotoxic activities, while the other compounds showed no notable cytotoxic activities, which indicated that the hydroxylation of C-3 or the open-ring structure increased the flexibility in the macrocyclic lactone ring and might contribute to cytotoxic activities.[168] Subsequently, cytotoxic activity investigations of five other lasiodiplodins, *i.e.*, (12*E*,15*R*)-5-hydroxy-3-methoxy-16-methyl-8,9,10,11,14,15-hexahydro-1*H*-benzo[*c*][1]oxacyclodocecin-1-one (**183**), ethyl 2,4-dihydroxy-6-(8-oxononyl)benzoate (**205**), (*R*)-zearalenone (**199**), 2,4-dihydroxy-6-nonylbenzoate (**200**) and (*R*)-de-*O*-methyllasiodiplodin (**185**), against MMQ and GH3 cell lines confirmed the importance of the hydroxyl group at the C-3 position. In fact, (12*E*,15*R*)-5-hydroxy-3-methoxy-16-methyl-8,9,10,11,14,15-hexahydro-1*H*-benzo[*c*][1]oxacyclodocecin-1-one (**183**), which is characterized by a methoxy moiety instead of a hydroxyl group at the C-3 position, was inactive. Furthermore, comparing the activity of ethyl 24-dihydroxy-6-(8-oxononyl)benzoate and (*R*)-zearalane, it seems that carbonylation of position C-15 reduced the cytotoxic activities (Fig. 16).[168]

Some insights into the SAR of β-resorcylic acid derivatives have been provided studying the phytotoxicity of ten compounds obtained from *L. theobromae* GC-22. (15*S*)-De-*O*-methyllasiodiplodin (**207**), (14*S*,15*S*)-14-hydroxy-de-*O*-methyllasiodiplodin (**209**) and ethyl 2,4-dihydroxy-6-(8-hydroxyheptyl) benzoate (**202**) showed phytotoxic effects against *Digitaria ciliaris* in a dose-dependent manner, while (13*R*,14*S*,15*S*)-13,14-dihydroxy-de-*O*-methyllasiodiplodin had a weak phytotoxic effect, which suggested that a hydroxyl group at C-14 had a significant impact on the phytotoxic activity and the presence of an additional hydroxyl group at C-13 of the macrocyclic lactone ring resulted in diminished phytotoxicity. Similarly, the hydroxyl or carbonyl group on the side chain attached to C-7 plays an important role in plant growth activity because ethyl 2,4-dihydroxy-6-(4-methoxycarbonylbutyl)benzoate (**203**), isobutyl (*S*)-2,4-dihydroxy-6-(8-hydroxynonyl)-benzoate (**204**) and ethyl 2,4-dihydroxy-6-(8-oxononyl)benzoate (**205**) displayed enhanced elongation activity toward *D. ciliaris*.[171] This result has also been confirmed by testing the phytotoxic effect of (3*S*,7*R*)-7-hydroxy-13-*O*-methyl-de-*O*-methyllasiodiplodin (**206**) and (3*S*,7*R*)-9-etheno-7-hydroxy-13-*O*-methyl-de-*O*-methyllasiodiplodin (**193**). In fact, these compounds share the same skeleton but the double bond and a hydroxyl group at C-7 of (3*S*,7*R*)-9-etheno-7-hydroxy-13-*O*-methyl-de-*O*-methyllasiodiplodin (**193**) reduced the phytotoxicity.[165]

Another interesting correlation between chemical structure and bioactivity arises from preussomerins (Fig. 14) isolated from *L. theobromae* ZJ-HQ1, which have been evaluated for their cytotoxicity on A549, HepG2, HeLa, MCF-7 and HEK293T human cell lines (Table S1). Chloropreussomerins A (**150**) and B (**151**) and preussomerin D (**155**) showed significant activity against the A549 and MCF-7 cell lines, while preussomerins F, G, H and K (**156–159**, respectively) exhibited promising growth-inhibitory effects on the A549, HepG2, and MCF-7 cell lines.

According to these data, it seems that the cytotoxicity of preussomerins strictly depends on the substitution of ring A. In fact, preussomerins F, G, H and K showed the same level of cytotoxicity because they all contain a ketone carbonyl and epoxide at ring A, whereas preussomerins A (**152**) and C (**153**) and Ymf 1029 E (**161**), presenting a hydroxyl group at C-1 of ring A instead of a ketone carbonyl group, displayed weak or no cytotoxic activity against all five cell lines. Furthermore, chlorinated preussomerins showed stronger inhibitory effects against the five human cell lines, indicating that the chlorine group at C-2 was important for cytotoxicity.[159] The same researchers also tested some isolated preussomerins (Fig. 14) for their antibacterial activities, observing different levels of activity against Gram-positive bacteria and no activity against Gram-negative bacteria (Table S1). This result suggests that these compounds possess selective inhibition against Gram-positive bacteria.[159] Overall, the existing SAR data for preussomerins are insightful but far from comprehensive because these class features are highly complex and only a small subset has been investigated.

Steroidal metabolites from *L. pseudotheobromae* reveal a straightforward SAR framework. The new steroids (22*E*,24*R*)-4α,5α-epoxyergosta-9α,14β-dihydroxy-7,22-diene-3,6-dione (**220**), (22*E*,24*R*)-4α,5α-epoxyergosta-9α,14α-dihydroxy-7,22-diene-3,6-dione (**221**), 12α-hydroxyergosta-7,22,24(28)-triene-3-one (**222**) and 3β,12α-dihydroxyergosta-7,24(28)-diene (**223**), along with a known congener (22*E*,24*R*)-9α,14β-dihydroxyergosta-4,7,22-triene-3,6-dione (**224**) (Fig. 16) have been tested for their cytotoxicity against five human cancer cell lines (RKO, A549, HepG2, SU-DHL-2, and HL-60). (22*E*,24*R*)-9α,14β-Dihydroxyergosta-4,7,22-triene-3,6-dione (**224**) showed remarkable activity, whereas (22*E*,24*R*)-4α,5α-epoxyergosta-9α,14β-dihydroxy-7,22-diene-3,6-dione (**220**) only exhibited moderate activities. Comparing the structure and the cytotoxic activities of these compounds, it can be deduced that the epoxidation of the double bond at C-4 reduces the cytotoxic activity of these steroids, while the α-oriented OH at C-14 is essential for their cytotoxicity. In the same study, these compounds have been also evaluated for neuroprotective activity and 3β,12α-dihydroxyergosta-7,24(28)-diene (**223**) was found to be the most active *in vitro* on glutamate-treated SH-SY5Y cells.[191] The current SAR landscape is built on relatively small analogue sets, clearly indicating that future efforts should prioritize studies creating a bridge between chemical structure and biological activity. Hence, the SAR insights outlined in this section do not mark a definitive endpoint but rather provide the preliminary basis for a more focused chemical–biological framework of *Lasiodiplodia* secondary metabolism.

5 Biosynthesis

Secondary metabolites are produced by a sequence of chemical transformations catalysed by enzymes. Biosynthetic pathways can differ according to the (micro)organism. In fact, there are alternative routes that could lead to the production of the same or similar compounds.[202]

Biosynthetic research on *Lasiodiplodia* spp. metabolites has delineated that they are essentially produced by polyketide and shikimate pathways. Not all pathways are experimentally determined in *Lasiodiplodia* spp., but possible biosynthetic origins can be hypothesized based on known chemical reactions.

Most compounds produced by *Lasiodiplodia* spp. are polyketides, which, while structurally diverse, are obtained by successive rounds of decarboxylative Claisen condensations between a thioesterified malonate derivative and an acyl thioesterconstitute.[202]

The biosynthesis of some metabolites *via* the polyketide biosynthetic pathway has been demonstrated by the administration of $^{13}C/^{2}H$-labeled acetates to *Lasiodiplodia* spp. A possible biosynthetic pathway has been described for theobroxide (**1**) and its related compounds through the administration

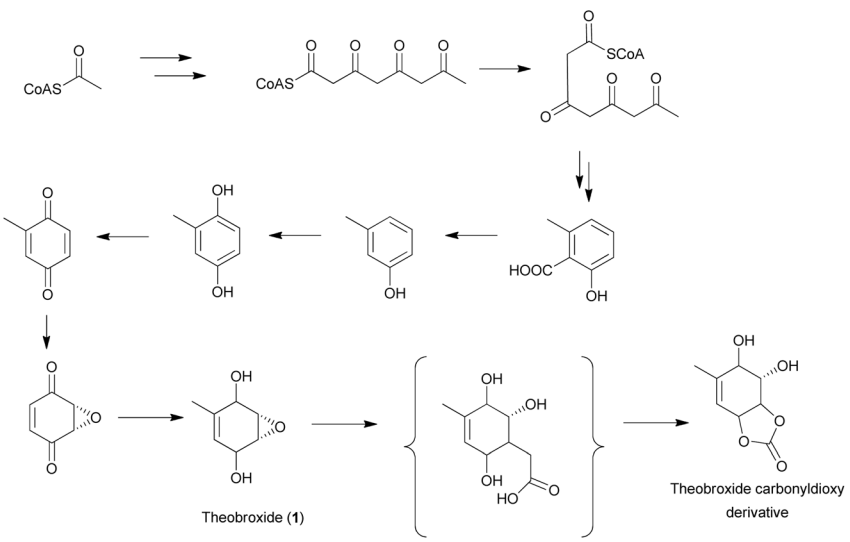

Fig. 19 Proposed biosynthetic pathway of theobroxide and its derivatives in *L. theobromae*.

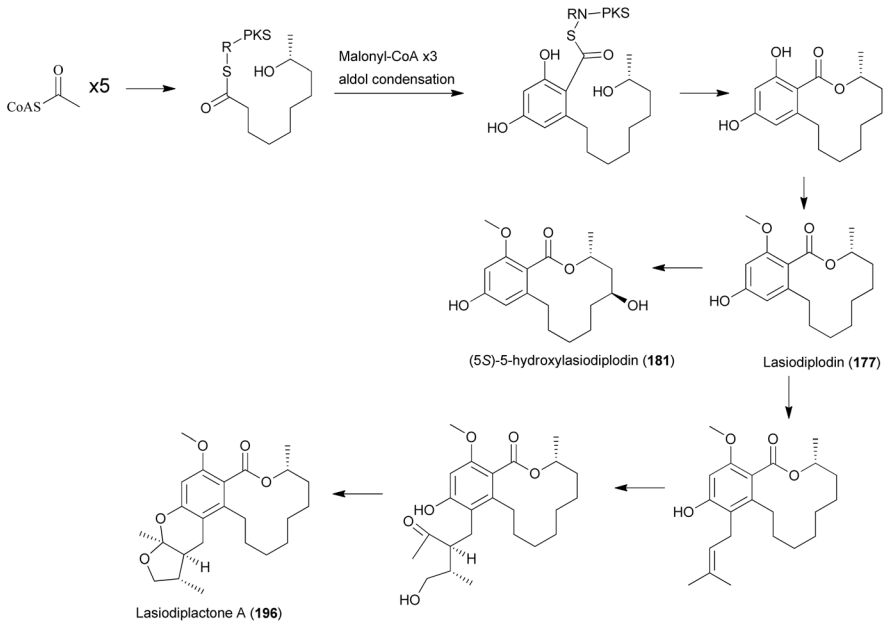

Fig. 20 Proposed biosynthetic pathway of lasiodiplodin and its derivatives in *L. theobromae*.

of ^{13}C-labeled acetates to *L. theobromae* to establish the tetraketide origins. By administering ^{2}H and ^{13}C-labeled acetates, the origin of the carbonate carbon of the theobroxide derivative was also determined (Fig. 19).[203]

Similar studies have been conducted to investigate lasiodiplodin (**177**) and its (5*S*)-5-hydroxylated derivative (**181**) by the administration of ^{13}C-labeled acetates to *L. theobromae*.[174,175] It has been demonstrated that these metabolites are biosynthesized *via* highly reduced acyl intermediates in the same

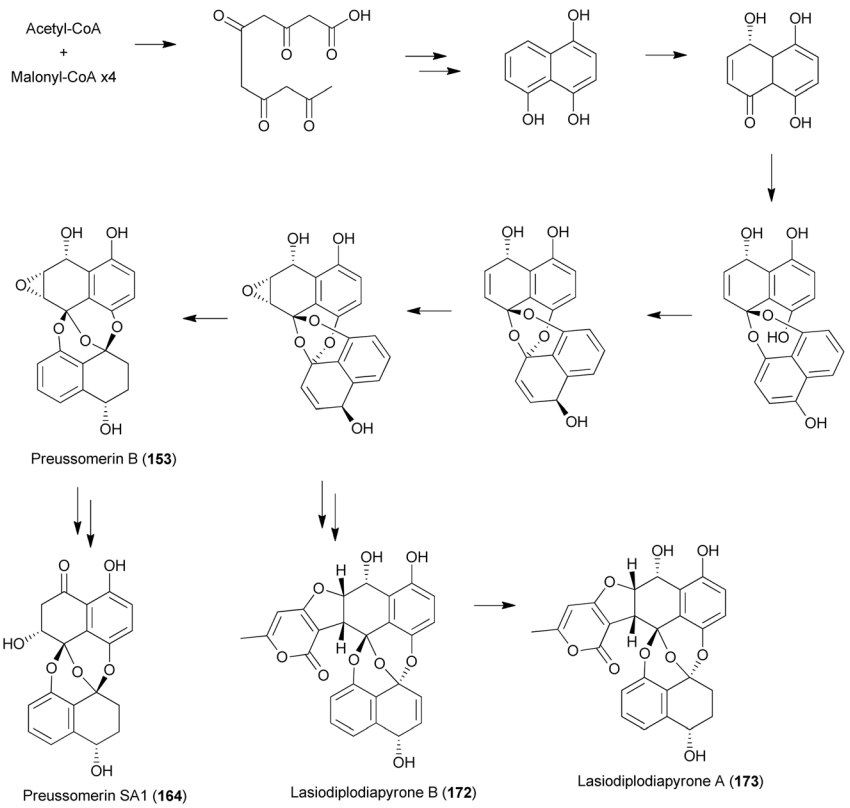

Fig. 21 Proposed biosynthetic pathway of preussomerins.

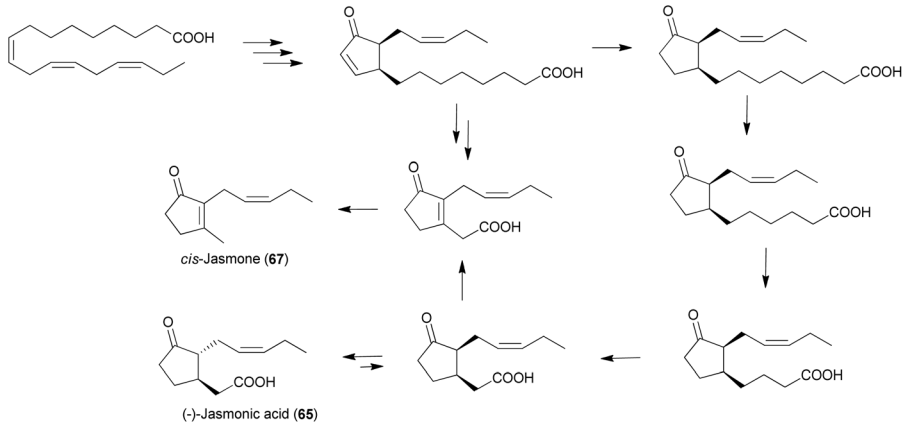

Fig. 22 Proposed biosynthetic pathway of (−)-jasmonic acid (**65**) and its derivatives.

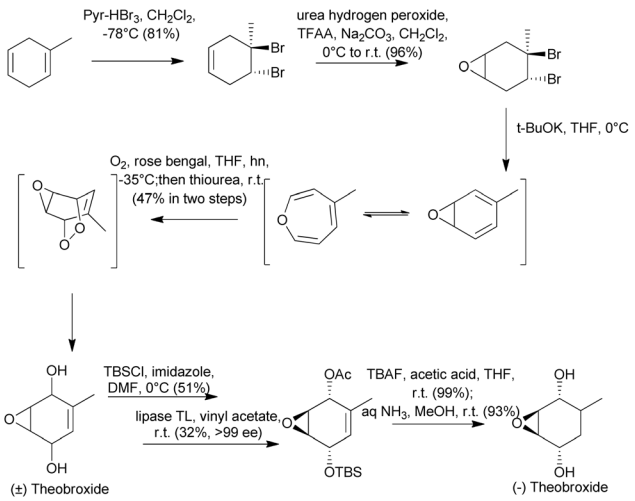

Fig. 23 Synthesis of theobroxide (**1**).

manner as other resorcylic acid derivatives (Fig. 20). An extension of this biosynthetic pathway has been proposed to generate lasiodiplactone A (**196**).[170]

Based on biosynthetic knowledge of preussomerins, Liang *et al.*[158] hypothesized the biosynthesis of lasiodiplodiapyrones A and B (**172** and **173**), two adducts of an α-pyrone and a polyketone obtained from *L. pseudotheobromae* 414-JZ-40, respectively, along with some congeners (Fig. 21).

There is extensive literature on the detailed mechanism of (−)-jasmonic acid (**65**) biosynthesis in plants starting from the oxygenation of α-linolenic acid. It is interesting that the cyclization mechanism in *L. theobromae* appears to be identical to that in plants. In fact, it is demonstrated that (−)-jasmonic acid is synthesized *via* a fatty acid synthetic pathway in *L. theobromae*, which is supported by ^{13}C labeling experiments. The incorporation of a synthetic ^{2}H-labeled linolenic acid into isojasmonic acid indicates that (−)-jasmonic acid biosynthesis in *L. theobromae* is similar to that of plants, differing only in the facial selectivity of the cyclopentenone reduction (Fig. 22).[204] It was reported that the biosynthetic pathway of *cis*-jasmone (**67**) in plants proceeded using (−)-jasmonic acid as a biosynthetic intermediate (Fig. 22). By using a combined approach involving feeding the fungus deuterium-labeled compounds and GC-MS analysis, the *cis*-jasmone biosynthetic pathway in *L. theobromae* was elucidated.[135]

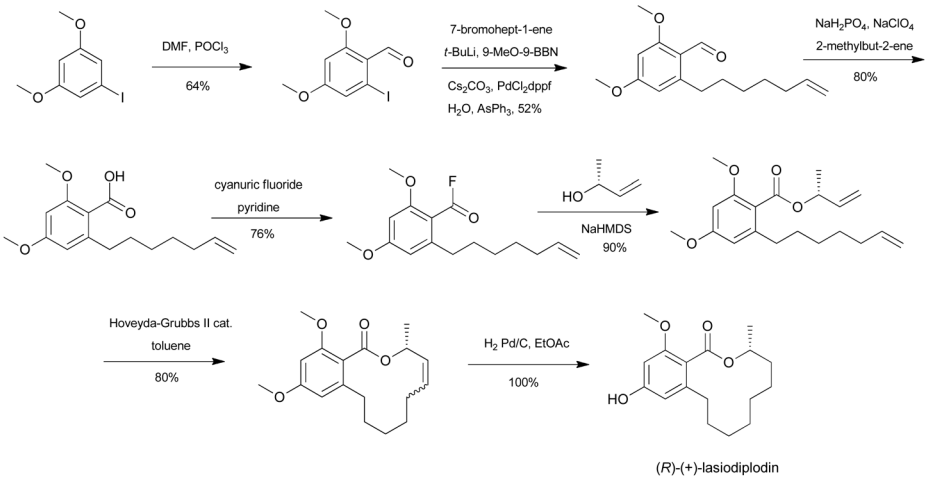

Fig. 24 Synthesis of (*R*)-(+)-lasiodiplodin (**177**).

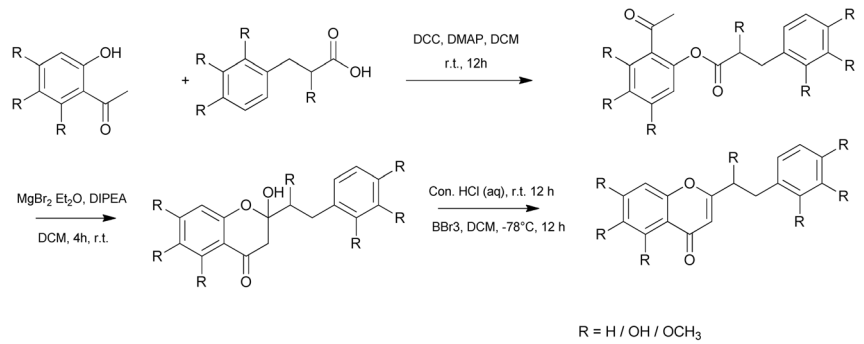

Fig. 25 Synthesis of 2-(2-phenylethyl)chromones.

The shikimate pathway is the metabolic process responsible for the biosynthesis of the aromatic amino acids: phenylalanine, tyrosine, and tryptophan. Microorganisms have evolved to assemble various secondary metabolites using these amino acids as building blocks.[202]

Indole-3-carbaldehyde (**55**) and indole-3-carboxylic acid (**56**) are produced by several microorganisms including *Lasiodiplodia* spp. It has been suggested that tryptophan was converted to indole-3-carboxylic acid *via* indole acetic acid in microorganisms, while some plants can directly metabolise L-tryptophan to indole-3-carboxaldehyde, which is further converted to indole-3-carboxylic acid. By analysing the metabolic intermediates of *Lasiodiplodia* sp. ME4-2, an indole acetic acid-independent route has been hypothesized,[205] while based on the metabolic investigation of cultures of *L. citricola* ALG 111, indole-3-carboxylic acid was detected along with indole acetic acid,

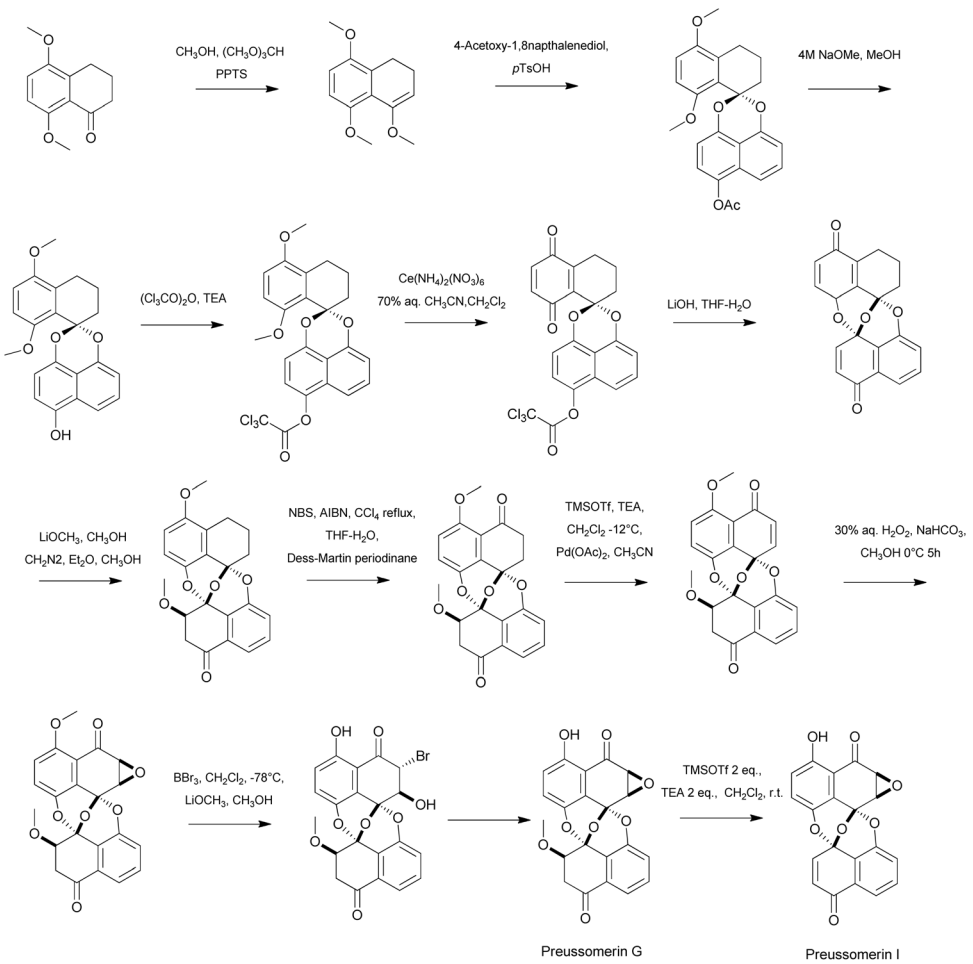

Fig. 26 Synthesis of (±)-preussomerin G (**157**).

suggesting that it was biosynthesised from tryptophan *via* the indole acetic acid pathway.[84]

6 Synthetic strategies

Owing to their unique structural features and interesting bioactivities, *Lasiodiplodia* spp. secondary metabolites have attracted attention from organic chemists to develop strategies for their synthesis. Many papers are available for a detailed description of synthetic approaches and thus we will focus on recent advancements as examples of the huge work done on the synthesis of these natural products. The supply of fungal compounds could be very low, as in the case of theobroxide (**1**), an epoxy cyclohexene compound isolated from cultures of *Lasiodiplodia* spp. showing potato micro-tuber-inducing activity and phytotoxicity (Table S1). Hence, an efficient synthesis of theobroxide has been implemented starting with the commercially available 1-methylcyclohexa-1,4-diene and the singlet oxygen oxidation of arene oxide as the key step.[206] The optical resolution of racemic theobroxide was also achieved with lipase (Fig. 23). Practically, this concise four-step approach is advantageous because it reduces the number of synthetic steps compared to previous, more laborious strategies for the synthesis of theobroxide.[207,208]

As reported in the previous sections, *Lasiodiplodia* spp. produce several β-resorcylic acid derivatives characterized by a scaffold that has been the target of several synthetic studies over the past 50 years.[209–212] The synthesis of (*R*)-(+)-lasiodiplodin (**177**) has been reported by several researchers, where most of them synthesised this compound starting from chiral materials (*e.g.*, enantiopure epoxides and alcohols), while some researchers synthesized the racemic form. Huang *et al.*[213] described the total synthesis of (*R*)-(+)-lasiodiplodin using catalytic asymmetric allylic substitution, sp^3–sp^2 Suzuki coupling and alkene ring-closing metathesis as key steps (Fig. 24). Recently, the protecting group-free synthesis of (±)-de-*O*-methyllasiodiplodin was reported.[214] This five-step synthesis proceeds in 42% yield from affordable starting materials (*i.e.* 9-decenoic acid). This efficient synthesis marks a significant improvement over previous strategies, which were limited by low yields.[212,215,216]

Substances with the 2-(2-phenylethyl)chromone scaffold from natural sources, including from *Lasiodiplodia* spp., have restricted availability, which has stimulated the development of synthetic approaches. Fig. 25 shows the synthesis of 2-(2-phenylethyl)chromones with hydroxylation and methoxylation as key mechanisms that contribute to their structural diversity.[217]

Due to their original chemical structures, preussomerins have stimulated many creative synthetic approaches.[156] The total syntheses of members of the preussomerin family have been achieved with the identification of the absolute stereochemistry of some of these natural products.[218,219] Fig. 26 shows the total synthesis of (±)-preussomerin G (**157**) leading to the bis-acetal ring system. In this elegant approach, the preussomerin skeleton is synthesized by a direct acetalization method as the first step, followed by additional oxidation, which is a possible biomimetic route. However, (−)-preussomerin G was synthesized by Barrett *et al.*[220] in 2002, achieving the first enantioselective route for accessing this family of natural products.

7 Concluding remarks

This review highlighted compounds discovered through the research activities conducted worldwide on *Lasiodiplodia* spp. The enormous chemical diversity of *Lasiodiplodia* metabolites (273 chemically defined compounds) and their bioactivities confirm the role of these compounds in fungal associations and adaptability. These compounds were classified by structure into fourteen distinct groups and an additional miscellaneous group containing compounds that show no structural affinity to the established classes. The biosynthetic capabilities of these fungi are quite original, as they constitute the only known source of certain unique natural products, such as theobroxide, lasiosan, lasiodiplodan, botryosphaeran, and lasiodiplodiapyrones A and B.

The ecological success of these fungi seems to be driven by their ability to produce secondary metabolites that enhance both host adaptability and infection mechanisms. This is further evidenced by the broad spectrum of bioactivities observed in *Lasiodiplodia* spp. metabolites, ranging from phytotoxic to antimicrobial and cytotoxic effects. However, some metabolites require an in-depth study to clarify their roles in fungal infection. In particular, *Lasiodiplodia* spp. are prolific producers of jasmonates, which warrant attention due to their roles as plant hormones. Further research is necessary to elucidate the mechanisms of fungal production for these established plant compounds.

When investigated, the biosynthetic pathways leading to the production of secondary metabolites in *Lasiodiplodia* spp. are similar to those of plants and other microorganisms, differing only in few details.

These metabolites have shown significant bioactivities suggesting the potential use of *Lasiodiplodia* spp. in biotechnological applications. Therefore, these fungi should be considered as biofactories with the potential to significantly expand the bioactive products currently known for use in various industrial sectors. For this reason, the synthesis of these compounds has been challenging since their initial discovery and continues to stimulate the creativity of organic chemists.

8 Author contributions

M. M. S.: conceptualization, writing – original draft, and writing – review and editing; M. M.: writing – review and editing and project administration; M. D. G.: writing – review and editing and project administration; and A. A.: writing – review and editing and project administration.

9 Conflicts of interest

There are no conflicts to declare.

10 Data availability

No primary research, software or code have been included and no new data were generated or analysed as part of this manuscript.

The data supporting this article (Table S1) have been included as part of the supplementary information (SI). See DOI: https://doi.org/10.1039/d5np00090d.

11 Acknowledgements

This work was carried out within the Program for the Finanziamento della Ricerca di Ateneo (FRA) 2022 dell'Università degli Studi di Napoli Federico II and by the funding from the Progetto PRIN: PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE: Bando 2022 PNRR Prot. P2022WXE4T, financed by the European Union Next-Generation EU (Piano Nazionale di Ripresa e Resilienza, PNRR).

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