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Review

The Thin Line between Pathogenicity and Endophytism: The Case of *Lasiodiplodia theobromae*

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Received: 18 September 2020; Accepted: 17 October 2020; Published: 21 October 2020

Abstract: Many fungi reported for endophytic occurrence are better known as plant pathogens on different crops, raising questions about their actual relationships with the hosts and other plants in the biocoenosis and about the factors underlying the lifestyle shift. This paper offers an overview of the endophytic occurrence of *Lasiodiplodia theobromae* (Dothideomycetes, Botryosphaeriaceae), a species known to be able to colonize many plants as both an endophyte and a pathogen. Prevalently spread in tropical and subtropical areas, there are concerns that it may propagate to the temperate region following global warming and the increasing trade of plant materials. The state of the art concerning the biochemical properties of endophytic strains of this species is also examined with reference to a range of biotechnological applications.

Keywords: endophytic fungi; mutualism; plant fitness; latent pathogens; *Botryosphaeria rhodina*; *Botryodiplodia theobromae*

1. Introduction

Endophytic fungi are plant-associated microorganisms that colonize the internal tissues of the host without inducing disease symptoms [1]. They represent a poorly understood endosymbiotic group of microbes that ought to be attentively considered by the scientific community, so as to provide comprehensive knowledge regarding their beneficial role and the actual extent of their interactions with plants.

A basic issue hindering studies on the ecological role of these microorganisms is represented by the reported endophytic occurrence of fungal pathogens. In fact, besides the cases where latency is a conspicuous phase of the disease cycle, there are more and more records of renowned pathogens found within asymptomatic hosts, for which an explanation is not immediately available [2–4]. Increasing and organizing the current knowledge on conditions associated with the occurrence of these ambiguous species is useful for a more conclusive assessment of their functions and impact on crops. This present paper offers an overview of a fungus which is mainly studied as a pathogen of tropical crops [4–6] but that is potentially able to spread as an endophytic associate of plants in the temperate zone.

2. Taxonomic and Phylogenetic Aspects

Lasiodiplodia theobromae (Pat.) Griffon & Maubl. (Dothideomycetes, Botryosphaeriaceae) is the accepted name of the species treated in this paper, prevailing over both the basionym *Botryodiplodia theobromae*

Pat. and the teleomorphic name *Botryosphaeria rhodina* (Berk & M.A. Curtis) Arx, after the introduction in mycology of the principle "one species—one name" [7]. Isolated and morphologically identified from a wide range of plant hosts [5,8], it represents the type species of *Lasiodiplodia* which, for many years, was treated as a monotypic genus within the Botryosphaeriaceae [9,10]. However, such a simplified taxonomy was destined to dramatically change with the advent of DNA sequencing. In fact, starting from the year 2004, phylogenetic analyses carried out in the course of studies on *L. theobromae* in novel pathosystems showed the existence of several clades, even within the pool of strains stored in mycological collections [11–14]. Evidence of a higher complexity emerged gradually, to such an extent that more than 30 additional species have been described to date, with some of them, such as *L. endophytica*, *L. gonubiensis*, *L. pseudotheobromae*, *L. thailandica* and *L. venezuelensis*, reported as endophytes [15–23]. Hence, it is likely that several previous findings might be incorrectly classified and that some more recent records are going to be re-examined. The application of high-throughput DNA metabarcoding as a biomonitoring tool is expected to provide a notable contribution in investigations concerning the endophytic occurrence of *Lasiodiplodia* [24].

To further complicate the issue, the existence of hybrid strains has been ascertained [15,25], which is also considered to have affected species identification. As an example, the taxon *L. viticola* Úrbez-Torres, Peduto & Gubler [26] has been shown to be a hybrid between *L. theobromae* and *L. mediterranea*; both these taxa are known on grapevine (*Vitis vinifera*), which most likely represented the venue of the hybridization process [15]. An assumption in biology considers as a species an organism whose population is reproductively isolated from other phylogenetically related populations [27]; hence, the existence of hybrids between several *Lasiodiplodia* spp. may imply that the taxa described so far are not stable. Indeed, further reassessments are to be expected, particularly in consequence of new combinations possibly stimulated by the circulation of plant material hosting genotypes which are potentially capable of hybridizing with autochthonous strains. In order to avoid further misidentifications, the use of multiple genes is recommended when considering the phylogenetic relationships of novel strains, along with direct referencing to the type strains [15,20].

Apart from the variation characterizing the genus *Lasiodiplodia*, phylogenetic relationships have also been evaluated in the species under discussion. Low genotypic diversity was observed in a study considering three populations from different tree species in Venezuela, South Africa and Mexico. A few predominant genotypes were encountered in the first two countries, without evidence of host specificity and in the presence of a very high gene flow between populations from different hosts. The geographic isolation was substantiated by the finding of unique alleles fixed in the different populations. Moreover, the existence of some genotypes that were widely distributed throughout the three countries, coupled with the evidence that pseudothecia are rarely produced in nature, suggests that reproduction is predominantly clonal [8]. A similar conclusion was reached in another phylogeographic study carried out on coconut palm (*Cocos nucifera*) in Brazil, where higher genotypic variation was observed in the northeast in connection with the local higher host diversity and a conjectured repeated introduction from Central Africa, regarded as the possible center of radiation of the species. Differences between genotypes were mainly ascribed to mutations [28].

In Cameroon, cocoa (*Theobroma cacao*) and *Terminalia* spp. are frequently grown together in a peculiar agri-sylvicultural system. A comparison between strains from these two known hosts of *L. theobromae* showed high levels of gene diversity and low genotypic differentiation, in the presence of high gene flow between isolates. The absence of a geographic substructure in these populations across the region where the study was carried out is indicative of the symmetrical movement of the fungus between these hosts. Unlike the case documented on grapevine, no evidence of hybridization was found with the closely related *L. pseudotheobromae*, which also occurs on these plants [29].

Finally, quite a simple genetic structure was once more pointed out in a broader study including strains of more varied origin. In fact, one or two main haplotypes across all genes were identified, and these genotypes were unrelated to both the hosts and the geographic area. Such overall uniformity clearly indicates that large-scale dispersal of *L. theobromae* is essentially derived from commerce and human activities [4].

3. Endophytic Occurrence of *Lasiodiplodia theobromae*

After having basically been studied as a plant pathogen responsible for serious damages of crops, particularly in tropical and subtropical regions [5,6], in the last three decades, the literature regarding *L. theobromae* has been substantially enriched by many reports concerning its endophytic occurrence on plant species which are quite heterogeneous in botanical terms (Table 1).

Table 1. Plant hosts of endophytic *Lasiodiplodia theobromae*. Species where the fungus has been also reported as a pathogen are underlined.

Source		Origin	Ref.
	Pinophyta		
Pinales, Pinaceae	*Pinus elliottii*	South Africa	[8]
	Pinus caribaea var. *hondurensis*	Venezuela	[8]
	Pinus pseudostrobus	Mexico	[8]
	Pinus tabulaeformis	China	[30]
Pinales, Taxaceae	*Cephalotaxus hainanensis*	China	[31]
	Taxus baccata	India	[32]
	Taxus chinensis	China	GenBank
	Magnoliids		
Magnoliales, Annonaceae	*Annona muricata*	Malaysia	GenBank
Piperales, Piperaceae	*Piper hispidum*	Brazil	[33,34]
	Piper nigrum	India	[35]
	Monocots		
Asparagales, Asparagaceae	*Dracaena draco*	Egypt	[36]
Asparagales, Orchidaceae	*Campylocentrum micranthum*	Costa Rica	[37]
	Cattleya sp.	Brazil	[38]
	Cymbidium aloifolium	India	[39]
	Dendrobium moschatum	India	[39]
	Encyclia fragrans	Costa Rica	[37]
	Epidendrum difforme	Costa Rica	[37]
	Epidendrum octomerioides	Costa Rica	[37]
	Epidendrum radicans	India	GenBank
	Eria flava	India	[39]
	Nidema boothii	Costa Rica	[37]
	Oncidium sp.	Brazil	[38]
	Paphiopedilum fairrieanum	India	[39]
	Phalaenopsis sp.	Brazil	[38]
	Pholidota imbricata	India	[39]
	Pholidota pallida	India	[40]
	Pleurothallis guanacastensis	Costa Rica	[37]
	Pleurothallis phyllocardioides	Costa Rica	[37]
	Sobralia mucronata	Costa Rica	[37]

Table 1. *Cont.*

	Source	Origin	Ref.
Asparagales, Orchidaceae	*Sobralia* sp.	Costa Rica	[37]
	Trichosalpinx blasdellii	Costa Rica	[37]
	Vanilla planifolia	India	[39]
Pandanales, Pandanaceae	*Pandanus* sp.	Thailand	[41]
Arecales, Arecaceae	*Calamus thwaitesii*	Sri Lanka	[42]
	Cocos nucifera	Brazil	[28]
		India	[43]
		Philippines	[44]
	Euterpe oleracea	Brazil	[45]
	Nypa fruticans	Malaysia	[46]
Poales, Cyperaceae	*Mapania kurzii*	Malaysia	[47]
Poales, Poaceae	*Cynodon dactylon*	India	GenBank
Zingiberales, Costaceae	*Costus igneus*	India	[48]
Zingiberales, Musaceae	*Musa* spp.	Malaysia	[49]
	Eudicots		
Proteales, Proteaceae	*Grevillea agrifolia*	Australia	[50]
Ranunculales, Menispermaceae	*Tinospora cordifolia*	India	[51]
Santalales, Santalaceae	*Viscum coloratum*	China	[52]
Saxifragales, Hamamelidaceae	*Distilium chinense*	China	[53]
Vitales, Vitaceae	*Vitis vinifera*	China	[54]
		Italy	[55]
Celastrales, Celastraceae	*Elaeodendrum glaucum*	India	[56]
	Salacia oblonga	India	[57]
Fabales, Fabaceae	*Acacia karroo*	South Africa	[58]
	Acacia mangium	Venezuela	[8]
	Acacia synchronicia	Australia	[50]
	Albizzia lebbeck	India	Genbank
	Arachis hypogaea	India	[56]
	Bauhinia racemosa	India	[56]
	Butea monosperma	India	[59,60]
	Cassia fistula	India	[56]
	Crotalaria medicaginea	Australia	[50]
	Dalbergia lanceolaria	India	[60]
	Dalbergia latifolia	India	[56]
	Glycyrrhiza glabra	India	[61]
	Humboldtia brunonis	India	[62]
	Indigofera suffruticosa	Brazil	[63]

Table 1. *Cont.*

Source		Origin	Ref.
Fabales, Fabaceae	*Libidibia (Caesalpinia) ferrea*	Brazil	[64]
	Lysiphyllum cunninghamii	Australia	[50]
	Mimosa caesalpinifolia	Brazil	[64]
	Ougeinia oojeinensis	India	[60]
	Phaseolus lunatus	Mexico	[65]
	Pongamia pinnata	India	[43]
	Saraca asoca	India	[66,67]
	Sophora tonkinensis	China	[68]
Malpighiales, Chrysobalanaceae	*Licania rigida*	Brazil	[64]
Malpighiales, Clusiaceae	*Garcinia mangostana*	Thailand	[69]
Malpighiales, Euphorbiaceae	*Croton campestris*	Brazil	[64]
	Croton sonderianus	Brazil	[64]
	Givotia rottleriformis	India	[60]
	Hevea brasiliensis	Malaysia	GenBank
		Peru	[70]
Malpighiales, Hypericaceae	*Hypericum mysorense*	India	[71]
Malpighiales, Rhizophoraceae	*Bruguiera cylindrica*	Philippines	[72]
	Ceriops tagal	China	GenBank
	Rhizophora mucronata	China	[73]
Malpighiales, Salicaceae	*Populus* sp.	China	[74]
Oxalidales, Elaeocarpaceae	*Elaeocarpus ganitrus*	India	GenBank
	Elaeocarpus tuberculatus	India	[56]
Rosales, Moraceae	*Artocarpus altilis*	Ecuador	Genbank
	Ficus opposita	Australia	[50]
	Ficus racemosa	India	GenBank
	Ficus trigona	Ecuador	GenBank
Rosales, Rhamnaceae	*Ziziphus xylopyrus*	India	[60]
Rosales, Ulmaceae	*Zelkova carpinifolia*	Iran	GenBank
Cucurbitales, Cucurbitaceae	*Momordica charantia*	China	[75]
Fagales, Fagaceae	*Quercus castaneifolia*	Iran	GenBank
Fagales, Juglandaceae	*Pterocarya fraxinifolia*	Iran	GenBank
Brassicales, Moringaceae	*Moringa oleifera*	Brazil	[64]
Malvales, Malvaceae	*Adansonia digitata*	Australia	[50]
		Cameroon	[15]
	Adansonia gregorii	Australia	[50]
	Adansonia za	Australia	[50]
	Gossypium hirsutum	India	[76]

Table 1. *Cont.*

Source		Origin	Ref.
Malvales, Malvaceae	*Grewia tiliaefolia*	India	[56]
	Helicteres isora	India	[60]
	Kydia calycina	India	[60]
	Theobroma cacao	Brazil	[77]
		India	[78]
	Theobroma gileri	Ecuador	[79]
Malvales, Thymelaeaceae	*Aquilaria malaccensis*	India	[80]
	Aquilaria sinensis	China	[81,82]
		Taiwan	GenBank
Myrtales, Combretaceae	*Anogeissus latifolia*	India	[60]
	Combretum leprosum	Brazil	[64]
	Lumnitzera littorea	Philippines	[72]
	Terminalia arjuna	India	[83,84]
	Terminalia bellerica	India	[56]
	Terminalia catappa	Cameroon	[85,86]
	Terminalia crenulata	India	[60]
	Terminalia ivorensis	Cameroon	[87]
	Terminalia mantaly	Cameroon	[86,87]
	Terminalia pterocarya	Australia	[50]
	Terminalia superba	Cameroon	[87]
	Terminalia tomentosa	India	[56]
Myrtales, Lythraceae	*Lagerstroemia microcarpa*	India	[60]
	Lagerstroemia parviflora	India	[60]
Myrtales, Melastomataceae	*Memecylon umbellatum*	India	[88]
Myrtales, Myrtaceae	*Calytrix* sp.	Australia	[50]
	Corymbia sp.	Australia	[50]
	Eucalyptus sp.	Australia	[50]
	Eucalyptus urophylla	Venezuela	[8]
	Eugenia uniflora	Brazil	[64]
	Psidium guajava	Venezuela	[89]
		Brazil	[64]
		India	[90]
		Nigeria	GenBank
	Psidium rufum	Brazil	[64]
	Syzygium cordatum	South Africa	[11]
	Syzygium cumini	India	[60]

Table 1. *Cont.*

Source		Origin	Ref.
Sapindales, Anacardiaceae	*Anacardium occidentale*	Brazil	[91,92]
	Astronium fraxinifolium	Brazil	[64]
	Mangifera indica	Australia	[93]
		Brazil	[91]
		Venezuela	[94]
		Costa Rica	[95]
	Myracrodruon urundeuva	Brazil	[64]
	Spondias mombin	Brazil	[64]
	Spondias sp.	Brazil	[64]
Sapindales, Burseraceae	*Boswellia ovalifoliata*	India	[96]
	Boswellia sacra	Oman	[97]
	Protium heptaphyllum	Brazil	[64]
Sapindales, Meliaceae	*Azadirachta indica*	India	[43]
	Khaya anthotheca	Ghana	[98]
Sapindales, Rutaceae	*Citrus sinensis*	USA	[99]
Sapindales, Sapindaceae	*Nephelium lappaceum*	Malaysia	GenBank
	Paullinia cupana	Brazil	GenBank
Sapindales, Simaroubaceae	*Ailanthus excelsa*	India	[100]
	Simarouba amara	Brazil	[64]
Ericales, Ebenaceae	*Diospyros montana*	India	[60]
Ericales, Lecythidaceae	*Barringtonia racemosa*	South Africa	[101]
	Careya arborea	India	[60]
Ericales, Sapotaceae	*Madhuca indica*	India	[102]
Icacinales, Icacinaceae	*Nothapodytes nimmoniana*	India	[103]
	Pyrenacantha sp.	India	GenBank
Boraginales, Boraginaceae	*Auxemma oncocalyx*	Brazil	[64]
	Cordia obliqua	India	[60]
	Cordia trichotoma	Brazil	[64]
	Cordia wallichi	India	[60]
Gentianales, Apocynaceae	*Alstonia scholaris*	India	[56]
	Catharanthus roseus	India	[90,104,105]
	Hancornia speciosa	Brazil	[106]
	Holarrhena antidysenterica	India	[59]
	Plumeria rubra	India	[107]
	Rauwolfia serpentina	India	[108]
Gentianales, Loganiaceae	*Strychnos potatorum*	India	[60]
Gentianales, Rubiaceae	*Coffea arabica*	Puerto Rico	[109]
	Ixora nigricans	India	[60]

Table 1. *Cont.*

Source		Origin	Ref.
Gentianales, Rubiaceae	*Morinda citrifolia*	India	[110]
	Psychotria flavida	India	[62,111]
	Psychotria sp.	Brazil	[64]
Lamiales, Acanthaceae	*Acanthus ilicifolius*	China	[112,113]
	Avicennia lanata	Philippines	[114]
		Malaysia	[115]
Lamiales, Bignoniaceae	*Jacaranda* sp.	Guyana	[116]
	Kigelia pinnata	India	[117]
	Radermachera xylocarpa	India	[56]
	Stereospermum angustifolium	India	[60]
Lamiales, Lamiaceae	*Gmelina arborea*	India	[60]
	Plectranthus amboinicus	India	[118]
	Pogostemon cablin	China	GenBank
	Premna tomentosa	India	[60]
	Tectona grandis	India	[60,119]
	Teucrium polium	Egypt	[120]
	Vitex negundo	India	[121]
	Vitex pinnata	Malaysia	[122]
Lamiales, Oleaceae	*Ligustrum lucidum*	Argentina	[123]
	Olea dioica	India	[56]
Solanales, Solanaceae	*Solanum melongena*	Brazil	GenBank
	Solanum nigrum	Egypt	[124]
	Solanum surratense	India	[125]
	Solanum torvum	India	[125]
	Withania somnifera	India	[125]
Apiales, Araliaceae	*Dendropanax laurifolius*	Malaysia	GenBank
Asterales, Asteraceae	*Bidens pilosa*	Egypt	[126]

The total number of 203 findings summarized in Table 1 is indicative of the widespread adaptation of *L. theobromae* to an endophytic lifestyle. They refer to as many as 189 plant species from 60 families, including representatives of the Pinophyta (seven species) along with the more numerous angiosperms. Among the latter, there are just *Annona muricata* and two *Piper* species in the Magnoliids, while Monocots and Eudicots are more common—particularly the families Orchidaceae (21 species) within the former, and Fabaceae (22 species), Combretaceae (12 species), Myrtaceae and Malvaceae (9 species each) within the latter grouping. Most of these plants are trees, which likely depends on both a preference of the fungus for lignified tissues and on the higher number of investigations on endophytes which have been carried out in forests and on woody hosts.

In geographical terms, a greater diffusion of *L. theobromae* is evident in tropical and subtropical countries (Figure 1), which is related to both the known prevalence of the fungus in this climatic zone and to the more consistent investigational activity in these countries, particularly India and Brazil, with, respectively, 81 and 32 records (ca. 40 and 16% of the total). Some reports are inaccurate and do not allow us to match the endophytic finding of *L. theobromae* with a definite host [127,128].

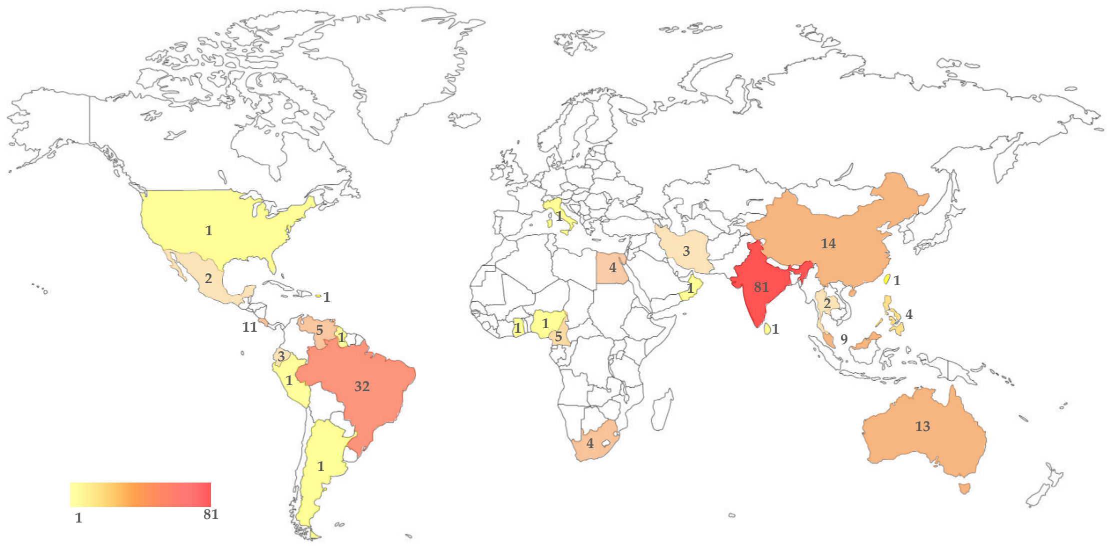

Figure 1. Geographical distribution of endophytic *Lasiodiplodia theobromae* as resulting from entries of Table 1. The color scale ranging from yellow to red is representative of the number of findings for each country.

4. Biological and Ecological Traits

As introduced above, endophytes are basically defined by their ability to spread in host tissues without inducing disease symptoms. However, the contraposition with pathogens is not so obvious, considering that many pathogens have a latent stage in their life cycle during which they are characteristically asymptomatic. The duration of this stage is very variable, and the pathogenic shift often depends on changes in the host susceptibility induced by several kinds of stress, which may reduce their tolerance or trigger a more aggressive behavior by the latent pathogen. For instance, plant stress is presented as a fundamental factor stimulating the pathogenic behavior of *L. theobromae* on dogwoods (*Cornus florida*), also considering the occasional failure of artificial inoculations during pathogenicity trials [129]. Genetic factors also actively influence the lifestyle shift of plant-associated fungi, as documented in a dedicated study disclosing repeated conversions during the evolutionary history of several species [130].

Members of the Botryosphaeriaceae are renowned as latent pathogens with a wide host range and geographical distribution [50,131]. Confirming this general feature, *L. theobromae* exerts such an ecological adaptability, particularly in tropical and subtropical regions [4,5]. However, the recent increasing trend in temperature may result in a major range expansion, placing more known and unknown hosts at risk.

Until recently, the incidence of latent pathogens has been underestimated, particularly in the trade of forest and horticulture plants and products; indeed, endophytes have been long disregarded in quarantine measures [131], which has enabled fungi to spread in plant germplasm circulating around the world [2,132]. With specific reference to *L. theobromae*, it has been conjectured that this fungus might have spread from Mexico to other subtropical countries through the trade of pine seeds [8]. Another hypothesis based on a phylogeographic approach considers the possible spread to South America from Africa to have repeatedly occurred as a consequence of human activities [28]. The availability of molecular techniques for the routine screening of plant material has increased the awareness that this risk has to be monitored [133]. In fact, besides considering pathogenic fungi of crops with an undefined latent stage [134,135], the European Food Safety Agency (EFSA) has recently started to consider the potential presence of disease agents occurring as endophytes in traded ornamental plants [136]. This concern is further supported by data gathered in this review, also considering that several hosts belong to widespread tree genera in boreal forests (e.g., *Pinus*, *Populus*, *Quercus*, *Taxus* and *Zelkova*). On the other hand, the accumulation of data on the occurrence of endophytes also provides an indication that some plants could be exempt. As an example, a recent review on the endophytic fungi of olive tree (*Olea europaea*), gathering all the available data concerning this important crop, has disclosed that, to date, there are no citations concerning *L. theobromae*, not only in the Mediterranean area but also in several tropical and subtropical countries where the plant has been introduced [3].

Many fungi reported for their endophytic occurrence are better known as plant pathogens. This is to be interpreted not only considering a more or less enduring latent stage within the disease cycle, as introduced above, but also with reference to a variable capacity by plant species to host certain fungal pathogens without showing symptoms of infection. Besides the more established concepts considering an improvement of host fitness in terms of growth promotion and protection against pests and pathogens, in the case of renowned disease agents, it has been conjectured that the capacity of a plant to host and promote their horizontal spread in the biocoenosis reflects a competitive advantage against other susceptible species [137]. This concept is quite appropriate for *L. theobromae*, which has such a high number of hosts as both a pathogen and an endophyte.

The problematic discernment of the real relationships with the host plant particularly emerged in our overview of the endophytic occurrence of *L. theobromae*. Indeed, defining this fungus as an endophyte in crops where it is known to cause disease (at least 46 plant species listed in Table 1, underlined) arouses a certain perplexity and raises the question of how to consider observations in the wild. The subject of plant pathology basically consists of diseases affecting crops or forest plants, and thorough assessments concerning fungal diseases of non-crop species are infrequent. In the absence of previous records and symptom descriptions, how can we be sure that a fungus isolated from "asymptomatic" tissues of a plant growing in whatever natural context is not exerting pathogenicity? It is worth observing that most of the plant species listed in Table 1 are not crops, and that for the majority of them, there is just a single finding, which is not at all sufficient for making a decision in this respect. Moreover, rather than being focused on the moment and circumstances of isolation, the issue should be considered with reference to the entire life cycle of the host plant: in this respect, how to consider reports of endophytic occurrence in centuries-old trees such as baobabs? [15,50].

Besides baobabs, there are more plants where it has been clearly demonstrated that the presumed endophytic occurrence is rather considered to refer to isolations carried out during the latent stage of the disease cycle. This is the case of cashew (*Anacardium occidentale*), where *L. theobromae* was recovered from healthy tissues at a distance of up to 80 cm from cankers caused by the same, and it was found to transmit through apparently healthy propagation material [92]. In other cases, the issue may be considered to have a "topographical" connotation, basically when the fungus exerts its pathogenic aptitude in some plant parts only. In fact, endophytic asymptomatic colonization of mango (*Mangifera indica*) shoots and branches has been shown to be prodromal to postharvest fruit rot [93,138]. In the case of *Aquilaria* spp. used for the production of agarwood, designating *L. theobromae* as an endophyte seems inappropriate too; in fact, resin formation is promoted as a reaction to an infection process which rather qualifies the fungus as a pathogen [139]. Likewise, internal infections by *L. theobromae* are reported to cause blue stain of wood after felling in *Pinus elliottii* [8], as well as in *Terminalia* spp. [87] and rubberwood (*Hevea brasiliensis*) [140]. It is worth considering that in similar cases observed on neem (*Azadirachta indica*) [141] and *Ficus insipida* [142], the occurrence of the fungus is merely referred to as a pathogenic association.

5. Bioactivities of Endophytic Isolates of *Lasiodiplodia theobromae*

Endophytes present potential for the exploitation of metabolites and enzymes. The biosynthesis of many secondary metabolites is often a response to environmental factors and fulfils different functions, such as defense, signaling and nutrient acquisition. Moreover, endophytes can influence the metabolism of the host and modify secondary metabolites by enzymatic steps of biochemical transformation [143].

Many studies have shown that endophytic fungi can synthesize bioactive products identical or similar to those produced by plants, representing an alternative source of some drugs and new useful medicinal compounds [144,145]. For this reason, many researchers have focused their attention on endophytes of medicinal plants, and many strains have been isolated which could be used for producing plant-derived drugs through fermentation. Among these fungi, *L. theobromae* particularly stands out for its ability to synthesize a high number of bioactive compounds [146]. The current panel of products is expected to further increase with reference to the many studies disclosing bioactive properties by endophytic strains of this species. Table 2 refers to investigations concerning endophytic strains of *L. theobromae* as a possible source of bioactive products, which sometimes are limited to assays carried out with culture filtrates.

Table 2. Bioactivities of endophytic isolates of *Lasiodiplodia theobromae*.

Bioactivity	Source	Sample tested	Ref.
Antibacterial	*Acanthus ilicifolius*	Secondary metabolites	[112]
	Aquilaria sinensis	Culture filtrate extract	[81]
	Calamus thwaitesii	Culture filtrate extract	[42]
	Dracaena draco	Culture filtrate extract	[36]
	Garcinia mangostana	Secondary metabolites	[69]
	Hancornia speciosa	Culture filtrate extract	[106]
	Humboldtia brunonis	Culture filtrate extract	[62]
	Madhuca indica	Culture filtrate extract	[102]
	Piper hispidum	Culture filtrate extract	[33]
	Terminalia arjuna	Culture filtrate extract	[84]
Antifungal	*A. sinensis*	Culture filtrate extract	[81]
	Avicennia lanata	Culture filtrate extract	[114]
	Bidens pilosa	Culture filtrate extract and secondary metabolites	[126]
	H. speciosa	Culture filtrate extract	[106]
	H. brunonis	Culture filtrate extract	[62]
	T. arjuna	Culture filtrate extract	[84]
Anti-inflammatory	*Acanthus ilicifolius*	Secondary metabolites	[113]
Antioxidant	*Catharanthus roseus*	Culture filtrate and mycelial extracts	[104]
	C. roseus	Silver nanoparticles	[105]
	T. arjuna	Culture filtrate extract	[84]
Antiprotozoal	*A. lanata*	Culture filtrate extract and chromatographic fraction	[115]
	Vitex pinnata	Secondary metabolites	[122]
Cytotoxic	*Acanthus ilicifolius*	Secondary metabolites	[112]
	A. sinensis	Culture filtrate extract	[81]
	B. pilosa	Culture filtrate extract and secondary metabolites	[126]
	C. roseus	Silver nanoparticles	[90]
	C. roseus	Culture filtrate and mycelial extracts	[104]
	Morinda citrifolia	Secondary metabolite	[110]
	Plectranthus amboinicus	Secondary metabolite	[118]
Enzymatic	*Azadirachta indica*	Isolate	[43]
	Cocos nucifera	Isolate	[43]
	Pongamia pinnata	Isolate	[43]
	Psychotria flavida	Isolate	[111]
	Terminalia catappa	Isolate	[86]
	Terminalia mantaly	Isolate	[86]
Heavy metal tolerance	*Boswellia ovalifoliata*	Isolate	[96]

Concerning the antibacterial activity, extracts produced by endophytic strains from the medicinal plant *Piper hispidum* were effective against four human pathogenic bacteria (i.e., *Enterococcus hirae*, *Escherichia coli*, *Micrococcus luteus* and *Staphylococcus aureus*) and showed good activity against *Salmonella tiphy* [33]. Antimicrobial activity was again displayed by endophytic strains from *Hancornia speciosa*, a plant native to Brazil, used to treat various pathologies [106].

Strains isolated from leaves, twigs and bark of *Terminalia arjuna* showed antimicrobial activity against *Bacillus subtilis* and *Aspergillus niger*, along with significant antioxidant properties [84]. The culture extract from an endophytic strain isolated from the mangrove *Avicennia lanata* in the Philippines was very active against the yeast *Saccharomyces cereviseae* but inactive against several Gram-negative and Gram-positive bacteria [114].

The culture extracts of endophytic strains from leaf and stem segments of *Humboldtia brunonis* were inhibitory against *Bacillus subtilis*, *S. aureus*, *Klebsiella pneumoniae*, *Proteus volgaris* and *Candida albicans* [62]. The crude extract from another endophytic strain isolated from *Madhuca indica* in India was found to be active against several common bacteria [102]. A strain isolated from *A. sinensis* showed low antimicrobial activity against microbial pathogens, particularly *Aspergillus famigatus*. This strain also displayed cytotoxic activity against some cancer cell lines [81]. Likewise, the culture extract of a strain from *Catharanthus roseus* exhibited cytotoxicity against the human cervical adenocarcinoma (HeLa) cell line [104].

The anticancer activity was particularly prominent when metal nanoparticles were prepared by exposing the endophytic fungus to metal salt solution. In fact, *L. theobromae* from leaves of *Psidium guajava* was used for the biological synthesis of silver nanoparticles, which provided powerful antitumor activity against human breast and lung cancer cells [90]. Silver nanoparticles were also prepared using an endophytic strain of *L. theobromae* isolated from *C. roseus*, inducing apoptosis in various types of cancer cells and promoting free radical scavenging [105]. These findings suggest that natural compounds produced by these isolates and incorporated into the nanoparticles have potential as a novel chemotherapeutic agent.

Finally, an endophytic strain of *Boswellia ovalifoliolata* is capable of growing in the presence of heavy metals (i.e., Co, Cd, Cu and Zn) in concentrations up to 600 ppm, showing that it may be used to remove heavy metals from solid substrates [96].

6. Secondary Metabolites and Enzymes of Endophytic *Lasiodiplodia theobromae*

As introduced above, the biological properties of culture extracts of endophytic *L. theobromae* might be linked to the capacity of the fungus to produce bioactive compounds (Figure 2). In fact, *L. theobromae* is a proficient producer of compounds belonging to different classes of secondary metabolites, such as diketopiperazines, indoles, jasmonates, melleins, lactones and phenols [146].

Biotic and abiotic stimuli influence the capacity of *L. theobromae* to grow and produce secondary metabolites, with implications for its physiology, lifestyle and pathogenic aptitude [146–148]. Studies on fungal genomes have shown that the capability of fungi to produce secondary metabolites has been underestimated, because many secondary metabolite biosynthetic gene clusters are silent under standard cultivation conditions [149,150]. In fact, different metabolomic profiles have been reported for *L. theobromae* strains according to variation in growth conditions, with reference to temperature [147,148], nutrient availability [151,152], presence of signal molecules [153] and incubation period [122].

Metabolomic investigations of *L. theobromae* have pointed out that some compounds are produced by endophytic strains only. This is the case of preussomerins and cloropreussomerins, compounds with an unusual structure isolated from the culture extract of a strain from leaves of the mangrove *Acanthus ilicifolius* and characterized for their cytotoxicity against five human cancer cell lines [112]. Moreover, endophytic strains from *Aquilaria sinensis* have been reported to produce 2-(2-phenylethyl)chromones, which are among the most abundant constituents of agarwood [154]. The coumarins meranzine and monocerin could be responsible for the antimicrobial activity of the culture extract of an endophytic strain from *Dracaena draco*, displaying characteristic inhibition zones against Gram-positive and Gram-negative bacteria [36].

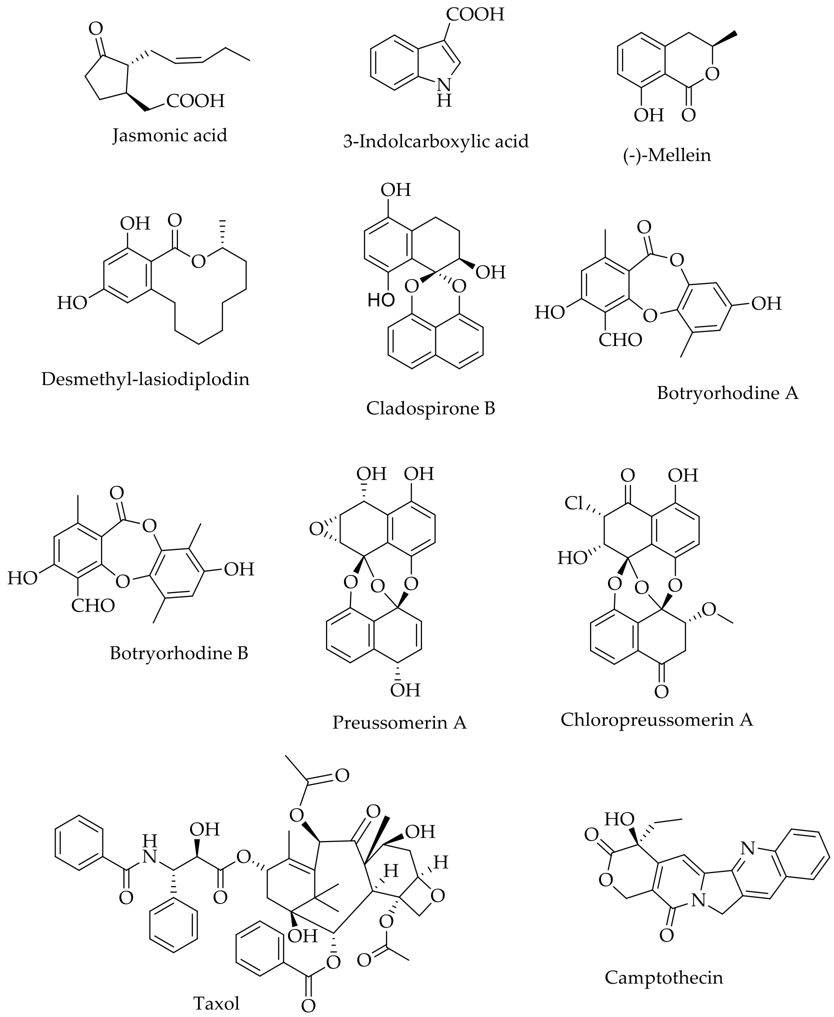

Figure 2. Representative secondary metabolites produced by endophytic *Lasiodiplodia theobromae*.

Lasiodiplodins were frequently, although not exclusively, reported as products of endophytic strains of *L. theobromae* [47,69,113]. These macrolides are relevant for a variety of biological properties including cytotoxic, antimicrobial and anti-inflammatory activities [69,155]. Within this class, lasiodiplactone A was obtained from a mangrove endophytic strain showing anti-inflammatory activity [113]. Furthermore, desmethyl-lasiodiplodin was isolated, together with cladospirone B and (-)-mellein, from the crude extract of a strain from leaves of *Vitex pinnata*. Interestingly, cladospirone B and desmethyl-lasiodiplodin showed good activity against *Trypanosoma brucei* [122].

An endophytic strain from the medicinal plant *Bidens pilosa* yielded four depsidones, botryorhodines A-D, and the auxin 3-indolecarboxylic acid, which are not exclusively produced by endophytic strains. Botryorhodines A and B show moderate cytotoxic activity against cervical cancer cells (i.e., HeLa) and antifungal activity against pathogenic fungi, such as *Aspergillus terreus* and *Fusarium oxysporum* [126].

The fact that two of the leading natural products, namely camptothecin and taxol, in cancer chemotherapy were originally extracted from plants is quite interesting from an applicative perspective [144]. The first compound has been detected as a secondary metabolite of strains isolated from the leaves and stem of *Nothapodytes nimmoniana* in the Western Ghats, India [103]. One of these strains (L-6) was investigated in depth with reference to the common phenomenon of attenuation of bioactive metabolite production in axenic cultures. It was found that its re-inoculation in the host promoted higher production of camptothecin, indicating that the fungus receives eliciting signals from the host tissues, or some factors which prevent silencing of the genes responsible for biosynthesis [156].

Taxol, the first billion-dollar natural antitumor product [157], has been reported as a secondary metabolite of several endophytic strains of *L. theobromae*, from *Taxus baccata*, *Morinda citrifolia*, *Salacia oblonga* and *Piper nigrum* [32,35,57,110]. Investigational activity carried out on the product extracted from these strains pointed out its ability to counteract the carcinogenic effects of dimethylbenzanthracene [158]. Moreover, valuable studies have disclosed the capacity by non-*Taxus* endophytic strains to produce the compound through a similar biosynthetic pathway as the one reported from the plant. In fact, the gene encoding 10-deacetylbaccatin-III-*O*-acetyltransferase, as well as the open reading frame of WRKY1 transcription factor, were cloned and sequenced and found to share high similarity with deposited sequences from *Taxus chinensis*, *T. cuspidata* and *T. celebica* [35].

Of great interest in endophytic *L. theobromae* is the production of phytohormones, such as indole derivatives and jasmonic acid analogues [146]. It is known that 3-indoleacetic acid and 3-indolecarboxylic acid are the most studied auxins regulating plant growth and development. These compounds have been frequently reported as fungal metabolites [144] and have also been documented as being produced by *L. theobromae* strains. The biological role of 3-indolecarboxylic acid has not been fully investigated, but some studies address its biosynthesis [159–161] and toxicity [147]. Several *L. theobromae* strains with different lifestyles are in vitro producers of jasmonic acid and analogues. Jasmonic acid is one of the most important signal molecules involved in several plant processes including seed germination, senescence and blooming. Hence, investigations of the bioactive properties of jasmonic acid and related compounds are essentially focused on their role in the interaction between host and pathogen.

The great ability of adaptation to different environments, the capacity to colonize a high number of hosts and the expression of high amounts of extracellular enzymes make *L. theobromae* a producer of relevant enzymes (Table 2) to be considered for biotechnological applications [162]. The most recognized extracellular enzymes used to penetrate the plant host include cellulases, proteases and lipases. Endophytic strains colonizing *C. nucifera*, *Pongamia pinnata* and *A. indica* exhibited great lipase activity [43]. Moreover, endophytic strains from *Terminalia catappa* and *T. mantaly* were found to produce amylases and cellulases [86]. Finally, *L. theobromae* isolated from *Psychotria flavida* turned out to be able to degrade irradiated polypropylene thanks to the production of laccases [62].

7. Conclusions

This overview of the endophytism of *L. theobromae* based on the literature published in the last three decades has pointed out its widespread occurrence in tropical and subtropical areas and the likeliness of further spread to regions with a temperate climate following the increasing trade of plant material. Hints concerning the biochemical properties are indicative of a certain degree of adaptation to the endophytic lifestyle, particularly deriving from the ability to synthesize bioactive products which may contribute to protection against biological adversities and improve plant fitness. However, the analysis of the available information also raises questions on whether the ability of *L. theobromae* to colonize such a high number of hosts is rather to be referred to as a fundamental pathogenic aptitude and whether a number of reports are actually referable to its interception during the latency phase of the disease cycle. Finding reasonable answers is clearly dependent on the analysis of additional data resulting from dedicated investigations in both natural and agricultural contexts.

Author Contributions: Conceptualization, R.N. and A.A.; writing—original draft preparation, M.M.S.; writing—review and editing, M.M.S., R.N. and A.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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