

Review



Mechanisms Underlying the Pathogenic and Endophytic Lifestyles in *Diaporthe*: An Omics-Based Approach

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Abstract: The genus *Diaporthe* encompasses important plant pathogens, endophytes, and saprobes that are widely distributed in tropical and temperate regions. An accurate detection and identification of plant pathogens not only allows correct disease diagnosis but also increases the accuracy of taxonomic ambiguities for fungal–plant interactions purposes. Multi-omics approaches applied to this genus may represent valuable tools to unravel molecular mechanisms involved in the infection processes. Additionally, omics can provide adaptation patterns that make pathogens thrive under changing environmental conditions, and insights into the dual pathogen–endophyte lifestyle. Therefore, all published data covered in this literature review represents an important contribution to deepen the knowledge on the importance of omics in fungal-plant interactions. This accumulating evidence will speed up the research on formulating new strategies to control plant pathologies, to assist in the exploitation of endophytes for their function in plant hosts, and to underline molecular factors of fungal pathogenicity and endophytism in the genus *Diaporthe*.

Keywords: endophytism; fungal–plant interactions; genomics; metabolomics; pathogenicity; proteomics; transcriptomics

1. Introduction

The genus *Diaporthe* is a species-rich phylogenetic group [1] that comprises several plant pathogens, endophytes, and saprobes [2]. As species of *Diaporthe* harbors phenotypic plasticity, their identification has relied mostly on the application of multilocus sequence analysis [3,4]. In this regard, the use of DNA sequences from type material provides the authentic biological material to investigate species boundaries in this genus [5,6]. However, the use of phylogenies to assess *Diaporthe* species boundaries remains a challenge for researchers [7], mainly due to the presence of high intraspecific and interspecific variability [3,8–10]. Moreover, species of this genus can be found cooccurring with other fungi (e.g., *Neofusicoccum, Pestalotiopsis*) on the same host under different lifestyles (e.g., endophyte, latent or harmful pathogen) [3,11], thus explaining the high number of taxa. Currently, the genus includes over 285 species supported by extype cultures and supplemented with DNA barcodes [1].

The early and accurate detection and identification of fungal plant pathogens is crucial to mitigate or prevent disease outbreaks, that may result in economic losses [12]. Therefore, the use of adequate phylogenetic methods is of paramount importance given that it increases the accuracy of taxonomic ambiguities [7] and provides insights for the discovery of natural products as well as additional information concerning the ecology and omics approaches among fungi [13]. For this reason, some authors have shown that besides phylogenetic analyses [1,3,9,14–16], the application of a cohesive approach comprising phylogenetic networks, studies on population genetic diversity, the detection

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Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/license s/by/4.0/). of recombination, and the Genealogical Concordance Phylogenetic Species Recognition principle (GCPSR) are fundamental approaches to circumscribe the boundaries of species in the genus *Diaporthe* [8,10,17].

Genome analysis has allowed the identification of pathogenicity traits in different fungal plant pathogens [18–20]. In the genus Diaporthe, genome sequencing of pathogens has revealed genes encoding for plant cell wall degrading enzymes and enzymes involved in toxin production [21–24]. However, the genomic resources of species of Diaporthe are still limited due to the low number of available genomes in public databases. This impairs transcriptomic, proteomic, and metabolomic profiling of Diaporthe during host infection. Additionally, multi-omics not only gives insights into the molecular basis of the pathogenicity strategies used by Diaporthe but also molecular traits underlying the dual lifestyle switching (endophytic-pathogenic). Accumulating evidence suggests that species of *Diaporthe* have the ability to shift between endophytic and pathogenic behavior, depending on the host species and environmental stresses [3,9,21]. Moreover, it is also recognized that effector proteins could underpin the Diaporthe pathogenic lifestyle [24] and shape the fungal lifestyle on a given plant [25-28]. Nevertheless, our understanding of the molecular determinants of fungal pathogenicity and endophytism remains scarcely explored [29]. Thus, this review aims to elucidate how omics can deepen the knowledge of the mechanisms involved in pathogenicity and lifestyle switching in species of Diaporthe.

2. Criteria Used for Selection of Studies and Search Strategy

This study was carried out aiming to be an up-to-date review to summarize current scientific data regarding the pathogenicity mechanisms of species of *Diaporthe*, well known as important plant pathogens and endophytes. Moreover, the importance of using omics approaches to provide insights into the dual lifestyle of *Diaporthe* species was also discussed in this review. Considering this, the literature review was organized to deepen the knowledge on the importance to identify putative effectors and their functions, other pathogenicity-related genes, secondary metabolites and metabolic pathways, and proteins in species of *Diaporthe*. This knowledge will be crucial to identify mechanisms that may be involved in plant–pathogen cross-talks and in the transition from the endophytic to the pathogenic lifestyle. All scientific literature selected was mainly focused on the last decade (2012 to 2022), representing more than 83% of the references listed (146 out of 176).

3. Species of Diaporthe: Pathogens or Endophytes?

Species of the genus *Diaporthe* are cosmopolitan and well known as pathogens on several agricultural crops, forest trees, and ornamental plants (Table 1), causing diseases including root and fruit rots, dieback, stem cankers, leaf spots, wilting, pod blights, and seed decay [15,30–32]. For example, cankers caused by *D. limonicola* and *D. melitensis* were reported on lemon trees [11], and *D. kongii*, D. *masirevicii*, and *D. ueckerae* were found causing stem and peg dieback on peanut trees (*Arachis hypogaea*) [33]. *Diaporthe ambigua*, *D. malorum*, *D. foeniculina*, *D. eres*, and *D. actinidiae* are associated with cankers, shoot blight, and fruit rot on apple tree (*Malus domestica*) [30,34,35].

Recent studies using molecular data have shown that while a few species are hostspecific, many others have an extensive host range [36,37]. For example, *Diaporthe ampelina* and *D. citri* are well-known pathogens associated only with *Phomopsis* cane and cankers of grapevines (*Vitis vinifera*) and melanose and gummosis on *Citrus* sp., respectively [27,38,39]. Similarly, *D. helianthi* is exclusively pathogenic to sunflower (*Helianthus annuus*), causing stem canker and twig blight [40] on crops in Europe, the USA, and Australia [41]. Other *Diaporthe* species are non-specific and infect a wide range of hosts [37,42]. For instance, *D. novem* has been reported as a pathogen on *Aspalathus linearis*, *Citrus* spp., *Glycine max*, *H. annuus*, and *Hydrangea macrophylla* [43]. Sunflower stem blight is also caused by *D. gulyae*, *D. kochmanii*, *D. kongii*, *D. stewartii*, *D. phaseolorum*, and *D*. *novem* [40,41]. Moreover, several *Diaporthe* species have been found associated with *Phomopsis* cane and leaf spot disease as well as cankers of grapevine [4,30,44].

Fable 1. Syno	psis of some	plant hosts	reported for	Diaporthe	species.
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Plant Hosts	<u>Creation</u>	Deferences	
Agricultural Crops	ultural Crops		
Prunus dulcis	D. amygdali, D. novem, D. foeniculina	[39,45–47]	
Malus domestica	D. malorum, D. leucospermi, D. eres, D. ambigua, D. foeniculina	[34,35,48]	
	D. foeniculina, D. rudis, D. leucospermi, D. eres, D. ambigua,		
Vaccinium corymbosum	D. crousii, D. amygdali, D. oxe, D. passiflorae, D. malorum,	[49–56]	
	D. hybrida		
Citrus spp	D. foeniculina, D. citri, D. citrishinensis, D. limonicola, D.	[11.21.57.58]	
	masirevicii, D. passifloricola	[11,21,07,00]	
Vitis vinifera	D. amygdali, D. celeris, D. rudis, D. ampelina, D. eres, D. gulyae,	[4.9.39.44.59]	
	D. hungariae, D. sojae, D. guangxiensis, D. novem	[]	
Corylus avellana	D. eres, D. amygdali, D. sojae, D. cercidis, D. hungariae	[32,60]	
Prunus persica	D. amygdali, D. eres, D. caryae, D. cercidis, D. hongkongensis,	[15.45.61]	
	D. unshiuensis	[,]	
Purus communis	D. infecunda, D. eres, D. terebinthifolii, D. phaseolorum, D. oxe,	[14.35]	
	D. sojae, D. amygdali, D. hongkongensis	[,]	
Gycine max	D. caulivora, D. longicolla, D. sojae, D. novem	[16,43,62,63]	
Helianthus annus	D. helianthi, D. gulyae, D. novem, D. caulivora, D. kochmanii,	[40,41,43,64]	
	D. kongu, D. stewartu		
Juglans regia	D. capcısı, D. eres, D. amygdalı	[32,65,66]	
Forest Trees			
Acacia spp.	D. accacigena, D. acaciarum, D. heterophyllae,	[67–69]	
	D. fraxini-angustifoliae	[0, 0)]	
Acer spp.	D. acericola, D. leucospermi	[37,70]	
<i>Eucalyptus</i> spp.	D. crousii, D. malorum, D. eucalyptorum	[71,72]	
<i>Fraxinus</i> spp.	D. silvicola, D. fraxinicola	[42,73]	
Pinus spp.	D. eres, D. rudis	[71]	
Quercus spp.	D. eres, D. foeniculina, D. rudis	[60,73]	
Ornamental Plants			
Camellia sinensis	D. amygdali, D. eres, D. hongkongensis, D. tulliensis, D. passiflorae	[74–76]	
Foeniculum vulgare	D. foeniculina, D. angelicae	[77]	
Hydrangea macrophylla	D. foeniculina, D. leucospermi, D. novem	[43,70]	
Lithocarpus glabra	D. amygdali, D. longicicolla, D. lithocarpus	[78]	
Rosa spp.	D. rosae, D. rosiphthora, D. rudis, D. eres, D. foeniculina	[3,79]	

Although species of *Diaporthe* are known as important plant pathogens and saprobes [3,7,9], they are also a major group of endophytes in stems and leaves of gymnosperms and angiosperms in tropical and temperate ecosystems [43,80]. Due to intercontinental trade of plant material, species of *Diaporthe* may behave as hitchhiking organisms [80] and are introduced into new areas as endophytes or latent pathogens acting as biotrophic at this stage. When the host is under stress conditions, the pathogen may switch to a necrotrophic stage inducing a phase of infection, and thus are called hemibiotrophs [6,81]. For example, it is assumed that *D. rudis* was imported to Chile via asymptomatic avocado fruit from California, causing then stem-end rot in avocados in Chile [82]. Moreover, some endophytes have been shown to act as pathogens, depending on the host and its health status [3]. *Diaporthe sojae*, previously found on *Citrus* as endophyte [83], was considered

genic to soybean [43] but endophytic in mangroves (Laguncularia racemosa) [84]. According to the literature, species of *Diaporthe* can be found with different lifestyles in nature. Nevertheless, it is still unknown whether environmental changes or the reduction in host's defense drive endophytes into pathogenicity [83]. Some authors stated that fungal lifestyle switches are a dynamic process [85]. Mishra et al. [86] concluded that the balance between nutrient requirements of a microorganism and plant defense is important in determining whether an organism turns endophytic or pathogenic. Several factors such as nutrition exchange, the genotype of host and the microbial organism, the microbial number, environmental changes, and microbial interactions may alter this balance [85,87– 89]. Thus, an imbalance may result in the microorganism success by surpassing plant immunity, leading to disease development [25,86]. For instance, Hilário et al. [90] showed that a water deficit regime imposed on blueberry plants, enhanced the transition from a latent to a pathogenic stage of *D. amygdali*. Moreover, it has been reported that high light intensity induces the pathogenicity of Diplodia mutila, an endophyte from the tropical tree Iriartia deltoidei [91]. Hoffman and Arnold [92] reported that cupressaceous trees in nonnative areas exhibited lower diversity of fungal endophytes than the native species. Moreover, the richness and diversity of endophytes in olive trees were also higher during the autumn season, as demonstrated by Materatski et al. [93], suggesting that the number of endophytes present in a given host may also define lifestyle switching.

Brader et al. [94] pointed out that endophyte strains from a certain host may not show symptoms on these plants but may be pathogenic on other hosts, suggesting that these strains are not true endophytes (those never causing disease) [25]. A recent investigation was carried out to distinguish between true endophytes and latent pathogens in diverse hosts [35]. Pathogenicity tests performed by the authors revealed that some species of *Diaporthe* did not cause disease and thus were considered as true endophytes. Nevertheless, other *Diaporthe* isolates were capable of causing disease, and therefore were characterized as latent pathogens [35]. In this regard, the presence of dual lifestyles in the genus *Diaporthe* still raises many doubts about their dynamics and behavior in plants. To better understand the dynamics of endophytism, it would be important to carry out comparative studies regarding gene expression and regulatory mechanisms in both plants and endophytes to understand how the same fungal species behaves as endophyte or pathogen [95].

4. Omics to Study Fungal Plant Pathogens

Recent advances in omics approaches such as transcriptomics and proteomics offer new opportunities to understand molecular mechanisms and to search for biomarkers expression for early diseases diagnosis (e.g., cancer, autoimmune diseases) [96,97]. Also in plant pathology, multi-omics (genomics, transcriptomics, proteomics, and metabolomics) can help mainly in the prevention and management of diseases [98]. The omics have been applied to elucidate the function of genes and the structure of the genome to provide insights into gene and protein expression and to understand the metabolic profiling of both the host and the pathogen during an infection process [99] (Figure 1). The application of omics in the genus *Diaporthe* is still poorly explored, although metabolomics has been widely applied to explore endophytic *Diaporthe* natural products for their potential applications in pharmacology [100]. Although the genus *Diaporthe* comprises important plant pathogens and endophytes, these species also have the ability to switch lifestyles [3,6,9]. Accordingly, multi-omics approaches could be crucial tools to unravel

- 1) Adaptation patterns of pathogens under changing environmental conditions.
- 2) Molecular traits underlying the infection processes.
- Patterns of endophytic fungal community and their implications for disease development.



Figure 1. Multi-omics approaches and obtained data for a thorough understanding of diverse aspects of plant pathogens and their cross-talks with plants.

4.1. Genomics

Since the sequencing of the first fungal genome, the yeast *Saccharomyces cerevisiae* in 1996 [101], advances in next-generation sequencing (NGS) technology have led to an increase in genomes [102], specifically from fungal pathogens that affect agriculture and forestry [103]. NGS is a rapid and high-throughput approach, and it is represented by different sequencing platforms such as AB SOLiD, Illumina HiSeq System, PacBio RS, and Oxford Nanopore Technology PromethION [104,105]. In 2011, the 1000 Fungal Genomes Project started with plans to sequence at least two reference genomes from each fungal family (<u>http://1000.fungalgenomes.org</u>; acceded on 5 February 2023). A search at the NCBI database (<u>https://www.ncbi.nlm.nih.gov/</u>; accessed on 10 February 2023) and the Genome Portal (<u>https://genome.jgi.doe.gov/portal/</u>; accessed on 10 February 2023) retrieved more than 12,200 and 2600 fungal genomes, respectively. Among these, over 11,550 genomes belong to the phylum *Ascomycota* that comprises the highest number of sequenced fungal genomes [106]. Despite the increasing number of fungal genomes over the last years, there are only a few genomes available in the genus *Diaporthe*. Table 2 sums up all species of *Diaporthe* with sequenced genomes deposited in NCBI and JGI databases.

Table 2. Synopsis of all *Diaporthe* strains with genomes sequenced. (Note: NA stands for 'not applicable' meaning that the genome is available at the JGI Portal but has no Project ID).

Species	Strain	Host	JGI Project	GenBank Accession Number	Sequencing Platform	References
	DA912	Vitis vinifera	NA	LCUC00000000	Illumina HiSeq	[107]
Diaporthe ampelina	S3MP	Commiphora wightii	-	LWAD00000000	Illumina HiSeq	[108]
Diaporthe amygdali	CAA958	Vaccinium corymbosum	-	JAJATV000000000	Illumina HiSeq	[22]
	DUCC20226	<i>Malus</i> sp.	-	JAJJOG00000000	PacBio Sequel and Illumina	-
Diaporthe aspalathi	MS-SSC91	Glycine max	-	LJJS0000000	Illumina HiSeq	[109]
Diaporthe batatas	CRI 302-4	Ipomoea batatas	-	JAHWGW000000000	Oxford Nanopore and PromethION	[105]
Diaporthe capsici	GY-Z16	Juglans regia	-	WNXA0000000	PacBio RSII	[65]
Diaporthe caulivora	D57	G. max	-	JAMPTR000000000	PacBio Sequel	[24]
Diaporthe cf. heveae	LGMF1633	-	1251927	-	-	-

Diaporthe destruens	CRI305-2	Ipomoea batatas	-	JACAAM010000000	Oxford Na- nopore and PromethION	[110]	
Diaporthe citrisiana	ZJUD30	Citrus unshiu	-	JADAZS00000000 JADWDH00000000	Illumina HiSeq	[21]	
Diaporthe citrichinensis	ZJUD34	C. unshiu	-	JADAZR000000000	Illumina HiSeq	[21]	
	NFHF-8-4	<i>Citrus</i> sp.	-	JACTAD00000000	PacBio Sequel	[111]	
Dignorthe citri	ZJUD2	C. reticulata	-	JADAZQ00000000	Illumina HiSeq		
Diuporine citri	ZJUD14	C. reticulata	-	JADAZP00000000	Illumina HiSeq	[21]	
	Q7	C. reticulata	-	JADAZO000000000	Illumina HiSeq		
Diaporthe eres (syn. D. phragmitis)	NJD1	Actinidia deli- ciosa	-	JACDXY000000000	PacBio RS	[112]	
Diaporthe eres (syn. D. vaccinii)	CBS 160.32	V. corymbosum	-	JAJATR000000000	Illumina HiSeq	[22]	
Diaporthe eres	Phoaprs 18- 02	Malus sp.	-	JAKJXL000000000	Illumina NovaSeq	[49]	
	Phoaprs 18- 03	<i>Malus</i> sp.	-	JAKJXM000000000	PacBio Sequel	[40]	
Diaporthe helianthi	7/96	Helianthus an- nuus	NA	MAVT02000001	Illumina MiSeq	[113]	
Diaporthe ilicicola	FPH2015- 502	Ilex verticillata	-	JALPVH000000000	Illumina and Oxford Nanopore	[114]	
Diaporthe inconspicua	LGMF1612	-	1251935	-	-	-	
Discoutles loss sizella	MSPL 10-6	G. max	-	AYRD00000000	Illumina HiSeq	[23]	
Diaportne iongicolia	TWH P74		-	JUJX0000000	Illumina HiSeq	[115]	
Diaporthe vexans	PV 4	Solanum melongena		JAJLLZ000000000	Oxford Na- nopore	[116]	
Diaporthe vochysiae	LGMF1583	Vochysia divergens	1251933	-	Pacbio	-	
Diaporthe sp.	DP-2020a	Sequoia semper- virens	-	JACVEP000000000	Illumina HiSeq	-	
Diaporthe sp.	HANT25	Hydnocarpus anthelminthicus	-	JACBFG00000000	Illumina HiSeq	[117]	

The low number of genomes and annotations available impairs researchers to unveil key genes involved in the infection process of *Diaporthe*, as well as mechanisms involved in the dual lifestyle (pathogen–endophyte). To bridge this, studies on the genome sequencing of *Diaporthe* species have focused on genomic signatures that allow them to successfully invade and colonize the host plant through the presence of:

- 1) Hydrolytic enzymes to degrade plant cell wall polysaccharides (e.g., pectins, celluloses, and lignins) to ensure a successful entry into the host [21–24].
- 2) Biosynthetic gene clusters encoding for toxic metabolites that injure plant cells and enhance disease progression. (e.g., fusicoccin A, fusarin, and ACT-toxin II) [22,23].
- 3) Cellular transporters of ions (e.g., zinc, sulfur, copper), molecules that enhance pathogenicity (e.g., peroxiredoxin, tetraspanin), and sugars from plant polysaccharides degradation (e.g., xylose, inositol, and glycerol) [22].

4) Pathogenicity-related genes (e.g., acid aspartate and aminopeptidase) and candidate effectors (e.g., carboxylesterases, CFEM-domain, and laccases) that facilitate the host to be infected and manipulate the host immune defense [22,24].

Moreover, genome-wide association studies could be implemented to identify the genomic regions potentially associated with aggressiveness, through the analysis of single nucleotide polymorphism (SNP) data [118]. The analysis of SNPs between pathogenic and non-pathogenic fungi/endophytes is also a promising tool for the identification of candidate effectors underlying the pathogenicity of species of *Diaporthe*, as well as to understand the ecological and evolutionary dynamics of plant pathogens [119].

The integration of omics approaches can also speed up the identification of putative effectors in the genus *Diaporthe* and the characterization of their virulence functions in their host plants. Effectors are secreted proteins by fungal pathogens that modulate and interfere with plant defense responses [120]. Recently, Mena et al. [24] defined a set of proteins considered within the secretome of six *Diaporthe* species through a comparative analysis of available genomes. Moreover, Hilário et al. [22] have also identified candidate effectors from two *Diaporthe* species, through sequencing and analysis of their genomes (Table 3). This suggests that the genomes of species of *Diaporthe* have a large array of candidate effectors involved in pathogenicity, and some of them are common to other *Diaporthe* pathogens while others are *Diaporthe*-specific [24]. Nevertheless, future studies should be undertaken aiming to reveal effector functions during the infection process and to understand how effectors alter plant physiology, thus underpinning *Diaporthe* lifestyles [121]. Overall, genomic studies on *Diaporthe* intend to deepen the knowledge on:

- 1) Ecological selection and adaptation of species of *Diaporthe* to degrade the available biomass as carbon source [22–24].
- 2) Gene functions related to pathogenicity [22,24].
- 3) Phylogenomic studies to offer insights into phylogenetic inference of *Diaporthe* [21,102].
- Genetic basis for multi-omics analyses to provide a thorough overview on plantpathogen interactions [19,24,122–124].

Species	Effector Candidate	Effector Location	References
	glycosyl hydrolase family 61	Apoplastic	
	aldehyde reductase 1	Apoplastic	
	putative cfem domain-containing protein	Cytoplasmic	
	putative metalloprotease	Apoplastic	
	murein transglycosylase	Apoplastic	
D. amygdali	acetyl xylan esterase	Apoplastic	[22]
	putative cerato-ulmin	Apoplastic	
	putative gas1-like protein	Apoplastic	
	putative secreted aspartic proteinase precursor	Apoplastic	
	Pectate lyase H	Apoplastic	
	glycosyl hydrolase family 61	Apoplastic	
	sterigmatocystin biosynthesis peroxidase stcC	Apoplastic	
	pectate lyase F	Apoplastic	
	putative 1,4-beta-D-glucan cellobiohydrolase A	Apoplastic	
D. capsici	putative proline-rich antigen	Apoplastic	[24]
	chitin deacetylase	Apoplastic	
	xylanase G1	Apoplastic	
	putative chitin binding protein	Apoplastic	

Table 3. Overview of some effector proteins identified in the genomes of species of Diaporthe.

	putative mannose binding	Apoplastic	
	putative gas1-like protein	Apoplastic	
	glycoside hydrolase family 11 protein	Apoplastic	
	Cell wall glyco protein	Cytoplasmic	
	Poly(rC)-binding protein 4	Cytoplasmic	
	putative sterigmatocystin biosynthesis peroxidase stcC	Apoplastic	
	putative proline-rich antigen	Apoplastic	
	putative cytochrome p450	Apoplastic	
	xvlanase G1	Apoplastic	
	glycoside hydrolase	Apoplastic	
D. caulivora	pectate lyase	Apoplastic	[24]
2	pertidase S41 family protein	Apoplastic	[]
	chitin deacetylase	Apoplastic	
	putative aldebyde debydrogenase	Apoplastic	
	putative aldenyue denyurogenase	Apoplastic	
	pectate lyase r	Apoplastic	
	putative 1,4-beta-D-glucan centrology arolase A	Apoplastic	
		Apoplastic	
	Glucan endo-1,3-beta-glucosidase	Apoplastic	
	putative 1,4-beta-D-glucan cellobiohydrolase A	Apoplastic	
	putative sterigmatocystin biosynthesis peroxidase stcC	Apoplastic	
	cholera enterotoxin subunit A2	Apoplastic	
D. citri	pectate lyase	Apoplastic	[24]
	polysaccharide lyase family 3 protein	Apoplastic	[]
	Chitin binding protein	Apoplastic	
	Acetylxylan esterase-like protein	Apoplastic	
	pectate lyase F	Apoplastic	
	xylanase G1	Apoplastic	
	putative riboflavin-aldehyde forming enzyme protein	Apoplastic	
	pectate lyase	Apoplastic	
	NPP1 domain-containing protein	Apoplastic	
	xylanase G1	Apoplastic	
	cellulose binding CEL1	Apoplastic	
	putative pectate lyase F	utative pectate lyase F Apoplastic	
D. aestruens	Poly(rC)-binding protein 4	Apoplastic	[24]
	chitin deacetylase	Apoplastic	
	ribosomal protein s17	Cytoplasmic	
	Protein CAP22	Apoplastic	
	fungal cellulose binding domain-containing protein	Apoplastic	
	pectate lyase	Apoplastic	
	Acetylxylan esterase 2	Apoplastic	
	putative glutamine-serine-proline rich	Apoplastic	
	putative rhampogalacturonan acetylesterase	Apoplastic	
Deres (sun D	vylanase (-1	Apoplastic	
nhraomitis)	Protoin CAP22	Apoplastic	[24]
phragmitis)	lytic polycaccharide monooyygenase	Apoplastic	
	ny ne porysacchanice monooxygenase	Apoplastic	
	peciale lyase r	Apoplastic	
	putative promie-ficit antigen	Apoplastic	
	chun deacetylase	Apopiastic	

D. eres (syn. D. vaccinii)	putative metalloprotease carbohydrate-binding module family 50 protein putative glycoside hydrolase family 61 protein acetylxylan esterase putative ricin b lectin putative pectate lyase b aldehyde reductase 1	Apoplastic Apoplastic Apoplastic Apoplastic Apoplastic Apoplastic Apoplastic	[22]
	putative npp1 domain	Cytoplasmic Cytoplasmic	
	putative pectate lyase	Apoplastic	
	disulfide-isomerase erp38	Cytoplasmic	
	polysaccharide lyase family 3 protein	Apoplastic	
	putative carbohydrate-binding module family 1 protein	Apoplastic	
	carbohydrate esterase family 5 protein	Apoplastic	
	starch binding domain-containing protein	Apoplastic	
	putative pectate lyase F	Apoplastic	
D longicolla	Acetylxylan esterase 2	Apoplastic	[24]
D. tongicottu	pectate lyase	Apoplastic	[24]
	cell wall protein PhiA	Apoplastic	
	xylanase G1	Apoplastic	
	cellulose binding CEL1	Apoplastic	
	fungal cellulose binding domain-containing protein	Apoplastic	
	Protein CAP22	Apoplastic	

4.2. Transcriptomics

The RNA-Seq technique has revolutionized the way in which transcriptomes are analyzed [125]. It promotes the understanding of gene expression under different conditions and allows for the discovery of new genes and transcription patterns, which helps to understand cell function and metabolic mechanisms [126]. As a result, it has been considered one of the most important applications of NGS technology, and one of the most important tools in plant pathology [125] since it allows to investigate the transcriptomic profiles of plant pathogens during infection [127,128]. As the interaction between plants and their pathogens is a dynamic process, these interactions should be analyzed as a dual process [127]. Hence, dual RNA sequencing allows to study host and pathogen transcriptomes simultaneously, detecting pathogen-specific transcripts as well as provides a more complete insight into the host defense mechanisms [129]. This approach has already been applied in studies of plant–pathogen interactions in crops such as grapevines [124,128]; peach [130] and potato [131]; medicinal plants [132]; and forest trees such as *Eucalyptus* sp. [133] and *Pinus* sp. [134].

However, the utilization of transcriptomics data is often hampered by the lack of annotations and genomes available, which is reflected in the scarce transcriptome studies, for example, in the genus *Diaporthe*. The few studies regarding the transcripts characterization in this genus are mainly based on quantitative PCR (qPCR). For example, Książkiewicz et al. [135] have used this technique to target genes on *Lupinus angustifolius* that confer resistance to *D. toxica*, the causal agent of lupinosis. Moreover, Elverson et al. [136] developed two qPCR assays to detect and quantify *D. helianthi* and *D. gulyae* on sunflower, the causing agents of *Phomopsis* stem canker. Hosseini et al. [137] have also established a multiplex qPCR to distinguish *D. longicolla*, *D. caulivora*, *D. eres*, and *D. novem* on soybean, which are responsible for seed decay, pod, and stem canker on this host. In another study, Fujiwara et al. [138] demonstrated that the qPCR assay they developed is useful to diagnose and quantify *D. batatas* and *D. destruens* in sweet potato, as they are the main causal agents of foot rot disease.

To our knowledge, Mena et al. [24] applied for the first time the dual RNA-Seq approach to the genus *Diaporthe* to evaluate how *D. caulivora* may affect soybean plants. The authors stated that the infected soybean with *D. caulivora* induces the reinforcement of cell walls, evidenced by the incorporation of phenolic compounds. Moreover, several defense genes were also upregulated, including those encoding a pathogenesis-related (PR) protein-1 (*PR-1*), a *PR-10*, a β -1,3-glucanase, two chitinases, two lipoxygenases, a phenylala-nine-ammonia lyase, and a chalcone synthase [24,62]. Given the cosmopolitan behavior of species of *Diaporthe*, their ability to infect a wide range of hosts and their different lifestyles (e.g., endophytes and pathogens), transcriptome analyses of both the host and the pathogen, and the validation of the differentially expressed genes (DEGs) should be considered to understand the regulatory networks and mechanisms involved in infection processes. Such an approach would thus contribute to unravelling host–pathogen interactions to provide helpful information for the development of disease control strategies [132-134, 139].

4.3. Proteomics

Profiling the protein expression can unravel the functions of different proteins by assessing the plant responses to environmental stresses, such as pathogen attack [99]. After the plant is stimulated by external stresses, their defensive response is rapidly generated, followed by changes in some physiological and biochemical characters (e.g., decrease in chlorophyl A and photosynthesis) [140]. For example, studies have demonstrated that *Arabidopsis* infected by *Fusarium* [141], rice infected by *Magnaporthe oryzae* [142], and strawberry leaves inoculated with *Colletotrichum* [143] showed an overexpression of peroxidase levels after pathogens infection, to scavenged reactive oxygen species (ROS). Additionally, PR proteins such as chitinases and plant β -1,3-glucanases are considered important components of plant defense mechanisms under a pathogen attack [144]. For instance, the above-mentioned proteins were upregulated in *Triticum aestivum* inoculated with *F. equiseti* [145] and in *Populus trichocarpa* after infection with *Botryosphaeria dothidea* [146].

When the fungus infects host plants, a series of effector proteins (e.g., cell wall degrading enzymes) are secreted into the host tissue to destroy intracellular components, interfering with their defense response [141,144]. The analysis of the proteome has been successfully made for some fungal plant pathogens. For instance, some studies have shown that cell wall degrading enzymes such as pectin, esterases, xylanases, pectate lyases, or galacturonases are upregulated in *L. theobromae* [143], *M. oryzae* [142], and *F. graminearum* [147], suggesting their pathogenicity on grapevines, rice, and barley, respectively. Moreover, the hydrolase glucan- β -glucosidase was found to be involved in the virulence of *C. higginsianum* [148] and *Alternaria alternata* [149]. Some effector proteins secreted by fungal pathogens, such as avirulence proteins (Avr), are delivered into the host plant, which have the potential to suppress pathogen-associated molecular patterns (PAMPs)-triggered immunity [150]. However, these pathogen-derived avirulence proteins are recognized by plant receptor proteins encoded by R genes, resulting in effectortriggered immunity that leads to fast responses [151].

As mentioned above, proteomics has been applied to unveil key proteins of several plant pathogens as well as those involved in plant defense under a pathogen attack. Nevertheless, no proteomic studies have been performed with members of the genus *Diaporthe* nor for their interaction with plants. As the proteome profiling during infection can identify specific proteins involved in plant disease resistance and pathogenicity processes [152], in-depth studies and comparative proteomics should be undertaken to reveal molecular mechanisms of *Diaporthe*–plant interactions as well as the susceptibility or resistance in plants. These studies will assist in the discovery of novel proteins that might be potential candidates for the enhancement of tolerance to fungal diseases.

4.4. Metabolomics

Currently, mass spectrometry (MS) has become a highly sensitive tool used for the identification and quantification of metabolites. Nuclear magnetic resonance (NMR) and types of mass analyzers are commonly used for metabolomic studies, such as capillary electrophoresis mass spectrometry (CE-MS), gas chromatography mass spectrometry (GC–MS), liquid chromatography mass spectrometry (LC–MS), and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) [153].

The increasing number of sequenced genomes and the scalable metabolomics approaches have largely expanded the access to the metabolite repertoire of fungi [154]. The awareness that fungi are a source of beneficial compounds came up after Sir Alexander Fleming in 1928 discovered penicillin [155]. This first broad-spectrum antibiotic was produced by the fungus *Penicillium notatum* (syn. *P. rubens*) and was considered as the 'wonder drug' of World War II [156]. After this event, the study of microorganisms as sources for antibiotics gave rise to the golden era for the discovery of natural products from fungi [157]. Species of the genus *Diaporthe*, for instance, are well known as producers of several compounds (e.g., polyketides, indoles, and terpenes) with potential applications in pharmacology and biomedicine [100].

Besides that, metabolomics research of plant pathogenic fungi has gained attention, since it allows the identification of metabolites, their functions, and metabolic pathways involved in pathogenicity [158–160]. Moreover, metabolomics profiling of host plants has also been performed to elucidate plant responses to abiotic and biotic stresses and to evaluate plant adaptations to such conditions [161]. For instance, Dickinson et al. [162] applied the LC–MS method to investigate metabolite changes of *Medicago tranuclata* under drought stress and infection with *F. oxysporum*. The authors stated that under pathogen infection, an increase in flavonoids, sucrose relocation from leaves to roots, and a decrease in organic acids were observed. Also, Jones et al. [163] used a meta-analytical method based on GC–MS/MS, LC–MS/MS, and NMR to evaluate rice plants at different time points after infection by *M. grisea*. These authors proposed that the production of a large amount of alanine caused by fungi may lead to cell death and thereby promoting *M. grisea* infection, suggesting that metabolomics may help evaluating the overall effects of pathogen infection on plant hosts [164].

It has also been suggested that metabolomic profiling in fungal–plant interactions provide important information for the early diagnosis of several fungal plant pathogens [161,164,165]. Hu et al. [164] used the GC–MS method to analyze the metabolic profiling of strawberry infected with *Botrytis cinerea* and identified biomarkers in the early stage of disease development. Moreover, Zeiss et al. [165] analyzed the metabolic profiling of tomato plants infected with *Ralstonia solanacearum* using the LC–MS method and detected metabolites that may be used as biomarkers for an early infection diagnosis (e.g., phenylpropanoids, phenolic acids, and flavonoids). Additionally, plant metabolomics can also help identify and link genes associated with resistance to fungal pathogens. For instance, Kage et al. [166] have also reported an increase in the metabolite coumaroy-lagmatine in a tolerant wheat variety to *Fusarium* head blight. The analysis of these compounds and their metabolic pathways paved the way for the detection of a gene (agmatine coumaroyl transferase) that confers resistance against *F. graminearum* [166].

Several studies have been focused to identify a wide range of metabolites produced by species of *Diaporthe* with biotechnological applications [100]. Nevertheless, there is still a lack of metabolomic studies on the interaction between species of *Diaporthe* and their hosts. Therefore, metabolomic approaches should be performed in *Diaporthe*-infected plants to elucidate the metabolic pathways involved in pathogenicity, as well as secreted metabolites as potential biomarkers for early disease diagnosis [158]. Moreover, unveiling metabolic features responsible for plant survival under stress conditions (e.g., pathogen attack) could facilitate crop improvement for biotic-stress tolerance, through the application of unique metabolites in formulations [99,161].

5. Omics to Underline Fungal Lifestyle Switches

Studies to understand the role of effector candidates during the infection process among species of *Diaporthe* could also reveal pathogenic lifestyles. Several studies have addressed the role of effectors to predict whether there are molecular differences between endophytes and pathogens [25]. For instance, Constantin et al. [26] found that strains of the endophytic *F. oxysporum* possessed fewer effectors than their pathogenic strains. On the contrary, Queiroz and Santana [167] revealed that both endophytic and pathogenic fungi share many of the proteins of their secretomes, and thus the difference between lifestyles were small. Genome analysis and the application of phylogenomics have revealed genes representing putative virulence factors involved in toxin production and wood degradation in members of the family *Botryosphaeriaceae* [168]. Moreover, genomics can also help understand the interactions between pathogens and endophytes as revealed for *Verticillium dahliae* [169]. Therefore, it is reasonable to state that using genome data could be an important approach to unveil virulence factors of endophytes in the genus *Diaporthe*.

Transcriptomics can also provide a deep understanding of the molecular traits that underline fungal lifestyle switching from endophytic to pathogenic state [166]. For instance, O'Connel et al. [28] have performed a comparative genomics and transcriptomics and showed that genes encoding secreted effectors, pectin-degrading enzymes, secondary metabolism enzymes, transporters, and peptidases are expanded in *C. higginsianum*. The authors stated that these genes are linked to pathogenic transitions: effectors and secondary metabolism enzymes are induced during the biotrophy (endophytic stage), whereas hydrolases and transporters are upregulated at the switch to necrotrophy (pathogenic stage) [28].

On the other hand, Zhou et al. [170] showed that the gene expression on both endophytic and saprophytic lifestyles of *D. liquidambaris* is strongly influenced by host environment. Additionally, it was suggested that mitogen-activated protein kinase (MAPK) signaling pathway may be involved in fungal lifestyle transition [170]. For instance, Becker et al. [171] found that the cell wall integrity (CWI) MAPK is a crucial signaling pathway for maintaining the mutualistic symbiotic interaction of *Epichloë festucae* with perennial ryegrass. On the other hand, the stress-activated MAPK pathway signaling and the production of ROS by the fungal NADPH oxidase (*Nox*) complex are key mechanisms that maintain a stable mutualistic association between *E. festucae* and ryegrass [172]. In this regard, when plants are infected by endophytic fungi, lacking functional *Nox* complexes or stress-activated MAPK signaling, the host can exhibit a slower growth while the fungus has a proliferative growth leading to a lifestyle switching from endophyte to pathogenic [173,174]. Such an outcome has been observed in *M. grisea* [175], *B. cinerea* [172], and *D. liquidambaris* [170].

Apart from studying the secondary metabolites involved in the pathogenesis, these compounds can also be potential determinants of endophytism [170]. For example, proteins involved in the biosynthesis of phenylalanine, tyrosine, tryptophan, sesquiterpenoids, and triterpenoids were upregulated in *D. liquidambaris* in the endophytic stage. Therefore, this suggests that endophytes may induce host plant synthesis of tryptophan and other alkaloid synthesis precursors, enhancing stress resistance of plants and limiting proliferation of endophytic fungi to a pathogenic stage [176]. Considering the dual lifestyle in the genus *Diaporthe*, omics technologies could be implemented in the future to gain insights into the candidate genes required to maintain the beneficial associations with plants and to understand the mechanisms underlying lifestyle switches.

6. Conclusions and Future Perspectives

Diaporthe is a species-rich genus that comprises endophytes and plant pathogens, causing disease on economically important crops. Omics technologies, such as genomics, transcriptomics, proteomics, and metabolomics, have become essential resources to understand plant–pathogen interactions for a sustainable agriculture. However, the limited

number of available genomes of *Diaporthe* hampers further research on key transcripts, proteins, and metabolites involved in species pathogenicity. Therefore, to speed up the identification of pathogenicity determinants and their functions for a better knowledge of plant–*Diaporthe* cross-talks, this review summarized the need to adopt omics technologies of both the host and the pathogen to

- Elucidate the broad spectrum of putative effectors underlying infection processes as well as to understand the ecological and evolutionary dynamics of plant pathogens.
- Identify differentially expressed genes to understand regulatory networks involved in infection processes, which can provide helpful information for the development of disease control strategies.
- 3) Unravel novel proteins that might be potential candidates for the enhancement of tolerance to fungal diseases.
- 4) Identify secreted metabolites and metabolic pathways to identify candidate biomarkers in the early stage of disease development.
- Provide evidence on the role of secreted effectors, pectin-degrading enzymes, secondary metabolism enzymes, MAPK signaling pathways and metabolites involved in pathogenicity as determinants of endophytism.

As stated in this review, the future application of omics techniques will surely enable new perspectives in deciphering *Diaporthe*–plant interactions. Incorporating omics data will improve our understanding of key molecular traits involved in host susceptibility/ resistant traits and in plant defense to offer novel crop protection opportunities. Moreover, multi-omics will also provide valuable information on pathogen virulence factors and the development of biomarkers and diagnostic kits, which will be fundamental for proper disease control and management. Despite the recognition of *Diaporthe* as the most common genera of endophytic fungi, up-to-date research should also be considered in the future. These should be focused on understanding which mechanisms and molecular traits underline the transition from an endophytic to a pathogenic lifestyle by addressing the following unanswered questions:

- 1) Are endophytic isolates location-specific and host-adapted?
- 2) Do isolates express multiple lifestyle?
- 3) Are endophytic and pathogenic fungi genetically differentiated?
- 4) What are the molecular differences between endophytes and pathogens?
- 5) Does an imbalance in the phyllosphere microbial community trigger life modes switching?

Therefore, future studies focused on the plant microbiome, for instance, would be an important approach to address the above-mentioned questions. This will offer insights into the endophytic community to unravel adaptation patterns in response to environmental stimuli, and to understand whether a dysbiosis may or may not affect the ability of fungi to switch life modes.

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