agronomy

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Review

An Overview of the Mechanisms Involved in Coffee-*Hemileia vastatrix* Interactions: Plant and Pathogen Perspectives

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Abstract: Coffee is one of the most consumed beverages in the world. It is also one of the most globally traded commodities. Coffee leaf rust (CLR), caused by the biotrophic fungus *Hemileia vastatrix*, is the most important disease affecting Arabica coffee growing worldwide, leading to significant yield losses if no control measures are applied. A deep understanding of the complex mechanisms involved in coffee-*H. vastatrix* interactions, such as the pathogen variability and the mechanisms governing plant resistance and susceptibility, is required to breed efficiently for durable resistance and design new approaches for crop protection. Here we summarize our current understanding across multiple areas related to pathogen infection, variability and candidate effectors, breeding for disease resistance, and the various components of the coffee immune system, by reviewing a comprehensive body of research on CLR and the advances recently made. We also update information about the defense responses activated by the application of plant resistance inducers, a promising alternative to fungicides in the control of CLR. Moreover, we identify and discuss future directions for further research.

Keywords: coffee leaf rust; rust variability; effectors; resistance; breeding; plant immunity; systemic acquired resistance

Citation: Silva, M.d.C.; Guerra-Guimarães, L.; Diniz, I.; Loureiro, A.; Azinheira, H.; Pereira, A.P.; Tavares, S.; Batista, D.; Várzea, V. An Overview of the Mechanisms Involved in Coffee-*Hemileia vastatrix* Interactions: Plant and Pathogen Perspectives. *Agronomy* **2022**, *12*, 326. https://doi.org/10.3390/agronomy12020326

Academic Editor: Adrian C. Newton

Received: 30 December 2021
Accepted: 21 January 2022
Published: 26 January 2022

1. Introduction

Coffee is not only a vital presence in the daily life of a significant share of the world's population, with consumption of over 3 billion cups of coffee a day, it is also the most valuable primary product in world trade, crucial to the economy of more than 50 countries, and constitutes the main source of livelihood for up to 25 million farmers and their families [1]. Traditionally, coffee has been viewed as a tropical commodity that links growing countries in the global South, along the so-called "bean belt" that lies between the tropics of Cancer and Capricorn, with consuming countries in the global North.

Coffee belongs to the genus *Coffea* of the family Rubiaceae and consists of over 100 species [2,3]. The two main cultivated species, *Coffea arabica* L. (Arabica) and *C. canephora* Pierre ex A. Froehner (Robusta) accounted in 2020, on average, for about 60% and 40% of the world's coffee production, respectively [4]. *Coffea liberica* Bull ex Hiern (Liberian coffee), a third beverage species, is cultivated worldwide but is insignificant in terms of global trade [5].

Coffee leaf rust, caused by the biotrophic fungus *Hemileia vastatrix* Berkeley and Broome, is one of the main limiting factors of Arabica coffee production [6–9] causing production losses of over $1 billion annually worldwide [10].

Since the 19th century historical first burst of CLR, which caused the eradication of coffee cultivation in Ceylon (now Sri Lanka), the disease spread through coffee-growing countries of Asia and Africa until 1950. In the Americas, CLR was first detected in Brazil in 1970 and dispersed progressively across the coffee plantations of other Latin American countries [11–13]. In Hawaii, CLR was reported for the first time in 2020 [14]. Nowadays, CLR is present in all the coffee growing regions. Furthermore, in the last decade, the epidemic resurgence of CLR known as "the big rust" impacted several countries across Latin America and the Caribbean on a level similar to the one observed in Ceylon [15–17]. This epidemic is causing losses of several hundred of million dollars, with extremely serious social consequences in the agricultural sector. It has been associated with changes in climatic conditions, the ecology of coffee farms, and recurring economic shocks [15,16]. Initially, there was some speculation that the epidemic might have been caused by the emergence of new, more aggressive rust races, but this hypothesis has not yet been confirmed [16,18].

H. vastatrix infects the lower surface of the leaves where it produces chlorotic spots preceding the differentiation of suprastomatal, bouquet-shaped, orange-coloured uredinia, leading to premature defoliation (Figure 1).

Figure 1. Coffee leaf rust symptoms and signs. (**A**) Chlorotic spots and uredosporic sori on the lower leaf surface; (**B**) an uredosporic sorum observed under the scanning electron microscope; (**C**) defoliation in coffee plants as a result of disease (right side), contrasting with resistant plants in the field (Brazil). Photos taken by the authors.

According to Rhiney et al. [18], defoliation is CLR's main effect, which reduces the plants' photosynthetic activity affecting the quantity of fruits and can influence coffee quality.

Coffee-*H. vastatrix* interactions are governed by the *Flor's* gene-for-gene relationship, and the resistance of coffee plants is conditioned at least by nine major dominant genes (S_H1–S_H9) singly or associated [11,19,20], although other major and minor genes may also be involved [11,21,22]. The use of coffee-resistant varieties is considered the most sustainable, efficient, and eco-friendly strategy to control this disease. Nevertheless, to improve the efficiency of the breeding process it is crucial to deepen our understanding of the complex mechanisms involved in the plant-pathogen interactions.

Plants have evolved highly complex defense mechanisms to protect themselves from various pathogens, with outcomes ranging from complete immunity, so called natural resistance or nonhost resistance, to susceptibility [23,24]. In addition to passive mechanisms, which include many preformed barriers such as waxy cuticles, rigid cell walls, and antimicrobial secondary metabolites [25], plants have evolved at least two lines of active defenses [26,27]. The first line provides basal defense against all potential pathogens and is based on the recognition of conserved microbe-associated or pathogen-associated molecular

patterns (MAMPs/PAMPs) and host danger-associated molecular patterns (DAMPs), by pattern recognition receptors (PRRs) that activate PAMP-triggered immunity (PTI). Plants PRRs are either surface-localized receptor kinases (RKs) or receptor-like proteins (RLPs) containing various ligand-binding ectodomains that perceive PAMPs. Importantly, PTI has the potential to fend off multiple microbes, pathogenic or not, due to the conserved nature of PAMPs (e.g., bacterial flagellin, fungal chitin) across species, genera, family, or class. Thus, PRRs can provide resistance to most nonadapted pathogens, as well as contribute to basal immunity during infection [28–30]. The second layer of defense is activated when a given pathogen-derived molecule, called "effector", is "specifically recognized" by plant receptor proteins encoded by R genes, resulting in effector-triggered immunity (ETI) that leads to fast and acute responses. Our understanding of ETI has evolved starting from the gene-for-gene theory [31], which describes the association between plants and their pathogens through the interaction of pathogen-derived avirulence (*Avr*) genes and plant-derived resistance (R) genes [26,32].

R genes mostly encode nucleotide-binding leucine-rich repeat receptor (NLRs) proteins. NLRs are modular proteins composed of several conserved domains that recognize effector proteins through different mechanisms. The direct recognition of the effectors by NLRs is described in the interaction between two flax NLRs and the rust *Melampsora lini* effectors [33]. In cases of indirect NLR-mediated effector recognition, either the NLR "guards" a host effector target and is activated upon detecting its molecular modification (the guard hypothesis), or a "sensor" NLR perceives the avirulent effector and activates a "helper" NLR that is responsible for triggering ETI [24,32].

Successful pathogens secrete effectors extracellularly or directly within the cytoplasm of the host cells, which can negatively interfere with PTI and ETI. As a result, plants are not able to defend themselves anymore and fall into the state of Effector-Triggered Susceptibility (ETS) [26,32].

Once activated, both PTI and ETI induce a downstream of similar defenses, such as rapid accumulation of reactive oxygen species (ROS), changes in cellular ion fluxes, activation of protein kinase cascades, production of stress-related hormones, cell wall modifications and changes in protein and gene expression [26,28,34]. These responses seem stronger and more prolonged during ETI when compared to PTI. ETI is typically associated with the hypersensitive reaction (HR), a form of programmed plant cell death localized at the infection sites [26,35]. HR is considered to be one of the most important factors in the restriction of the pathogen growth, particularly of obligate biotrophs [36,37] such as rust fungi, being responsible for race-specific resistance [38]. Despite their differences and particular features, the two-layered defenses (PTI and ETI) should be considered as a continuum resulting in the activation of an overlapping set of immune reactions [39].

Plants can also induce defense reactions to a broad range of pathogens due to prior exposure to pathogens or physical stress. This ability of plants to react to an invader by triggering local and systemic defense responses is known as systemic acquired resistance (SAR) [40]. It is considered one of the players in a multifaceted inducible defense system in plants, characterized by various signaling pathways and metabolic responses [41–43].

This review provides an overview of our current knowledge on the coffee-*H. vastatrix* interaction, mainly regarding pathogen infection and variability, the discovery of pathogen effectors, breeding for disease resistance, and multilayered host defense responses. This review also contains information about the coffee defense responses activated by the application of resistance inducers, nowadays used as a promising approach to integrate crop protection practices [44]. Emphasis is given to significant advances obtained over past decades through gene expression analysis and the application of various omics methodologies. We also discuss the main challenges for future research in this complex biological system.

2. CLR Causal Agent: Life Cycle and Biotrophic Infection Process

H. vastatrix (phylum Basidiomycota, class Pucciniomycetes, order Pucciniales) is a hemicyclic fungus producing urediniospores, teliospores and basidiospores, but only the

dikaryotic urediniospores, which form the asexual part of the cycle, reinfect coffee leaves successively and are responsible for the disease [7]. *H. vastatrix,* like other rust fungi, is an obligate biotroph, which means that it can only feed, grow and reproduce on its living host(s). It differentiates specialized infection structures called haustoria that have been linked to pathogen nutrient uptake from the host cell. Haustoria also appear to play essential roles in plant-fungus recognition and delivery of secreted effector proteins into the host cytoplasm for the establishment of a successful biotrophic relationship [45–48].

The *H. vastatrix* infection process begins by the adhesion of urediniospores to the lower surface of the coffee leaves followed by its germination and appressoria differentiation over stomata. Adhesion may be regarded as a necessary prerequisite to establish the fungus on the leaf for successful infection [49]. After adhesion of rust urediniospores to the plant surface, the development of infection structures is the result of a sophisticated host surface recognition system. The tip of the dicaryotic germ tube is able to follow topographical features of the plant cuticle and thus increase the probability of encountering a stomatal opening [49]. Esterases seem to be involved in *H. vastatrix* urediniospores adhesion and appressoria differentiation [50].

The appressorium is the first infection structure from which *H. vastatrix* is able to penetrate the coffee leaf tissues, reaching sequentially the stages of penetration hypha, anchor and haustorial mother cell, which gives rise to a haustorium, that starts by infecting the stomatal subsidiary cells. Fungal growth continues with the formation of more intercellular hyphae, including HMCs and haustoria, in the spongy and palisade parenchyma, and even the upper epidermis. At this stage, it is possible to observe macroscopic chloroses on the leaf's surface. Once the hyphae invade the substomatal cavities, they differentiate to form protosori, and about 3 weeks after the beginning of the infection urediniosporic sori (Figure 1) protrude through the stomata in a bouquet shape [7,20,51,52].

The development of the entire uredinial cycle depends on environmental conditions [7,18]. Urediniospore germination requires water and is optimal at about 24 °C; rain is the primary dispersal mechanism for spores. The time from initial infection to the production of a new sorus is shortened in higher temperatures. Thus, drier, cooler climates are not conducive for CLR spread, whereas warmer, humid climates favor an increase of urediospores (sporulation).

3. Rust Variability

The first indication of the adaptive capacity of *H. vastatrix* was the loss of resistance of *C. liberica* observed in Indonesia between 1880 and 1890, which contributed to the subsequent decline of Liberica coffee cultivation in that country [53]. The loss of resistance of Coorg Arabica variety in India alerted the occurrence of pathological shifts that led, from 1918 to 1920, to its replacement by Kent's Arabica variety, which maintained its resistance to rust for several decades [54]. In 1932, Mayne, in India, presented the first experimental evidence of physiological specialization of *H. vastatrix* by differentiating two races using laboratory inoculations: one only virulent to Coorg (race 1) and the other to both Coorg and Kent's (race 2) [55]. Afterwards, Mayne identified another two races with virulence to S.288 and S. 353 Arabica varieties [56].

Following the creation of the Coffee Rusts Research Center (CIFC, Centro de Investigação das Ferrugens do Cafeeiro) in Portugal in 1955, many samples of leaf rust and coffee genotypes were received from different regions of the world, assisting research of coffee resistance. Thanks to this work, the existence of Mayne's races was confirmed at CIFC, and about 55 additional rust races have been discovered until today [7,11,20,21,56–61]. These races have been identified according to the virulence or avirulence reactions they induce when inoculated on a set of 27 coffee differentials: clonal lines of 5 *C. arabica* selections, 16 tetraploid hybrids of *C. arabica* × *Coffea* spp., and 6 *Coffea* spp. selections [7,11,21,60]. *H. vastatrix* races are attributed to isolates with distinct and unique combinations of virulence genes as inferred by Flor's gene-to-gene theory and described as sequential Roman numerals in order of detection [19]. The race genotypes comprise virulence genes ranging from v_1 to v_9 in isolates derived from *C. arabica* and tetraploid interspecific hybrids,

whereas those that attack diploid coffee species are not known due to the unavailability of genetic studies in these hosts [7,11,20]. The genetic characterization and confirmation of these virulence loci has not been possible so far, mainly because, on one side, no sexual phase in *H. vastatrix's* life cycle has yet been identified, and on the other side, no direct link between phenotypic diversity and molecular diversity has been found. These limitations, together with the complexity and large size of *H. vastatrix´*s genome [62–64], have impaired further advances on the development of virulence diagnostic markers. Thus, the virulence profile characterization, particularly of isolates infecting Timor hybrid (HDT) derivatives, can only go as far as the available collection of coffee differential genotypes allows, leaving many genotypes incompletely identified [7,60]. For a long time, characterization of the population genetic variability in coffee rust was also intricated, as different studies reported different levels from low to high, but consistently no evidence of population structure could be found with respect to race, host or geographical origin [7]. Recent efforts in genomic research on coffee rust changed this paradigm, and for the first time three divergent genetic lineages were found, highly structured according to coffee hosts (C1 and C2, infecting diploid coffee species; and C3, infecting tetraploid coffee species), revealing footprints of introgression [65]. More recently, additional genomic data allowed further discovery of a well-resolved substructuring within the C3 lineage, which seems to follow a pattern of local adaptation [66]. With the likely increase of genomic resources in a short time, we might expect to improve our knowledge of population variability and virulence evolution and envision the future development of candidate diagnostic markers associated with rust pathotypes. Additionally, the first version of the core proteome of *H. vastatrix* urediniospores performed by nanoLC-MS/MS analysis has been presented [67]. Proteins were functionally annotated as being involved mainly in DNA integration, RNA-dependent DNA biosynthesis, proteolysis, translation, oxidation-reduction process, primary metabolism, nitrogen compound metabolism and macromolecule metabolic processes. The comparative analysis of the proteomes of the three rust races studied showed that 95% of the identified proteins (1780 out of 1874) were commonly detected among races. The identification of the protein factors (5%) that characterize each virulence profile is under analysis.

4. Mechanisms of Pathogenicity: The Search for *H. vastatrix* Effectors

The prediction of fungal effectors involved in plant interactions has been the focus of much attention by the research community working on plant diseases. Effectors are secreted proteins that move from the fungal to the host cells/tissues, where they induce or suppress plant defense responses since they modulate and interfere with the integrated plant immune system (including both PTI and ETI plant defense responses) [68]. Effector identification has the potential to speed up the selection of plant resistance genes and/or the removal of plant susceptibility genes in breeding programs of relevant agronomic varieties [69,70].

Fernandez et al. [71] obtained the first predict *H. vastatrix*'s secretome from *C. arabica* infected leaves by RNAseq. Two years later Talhinhas et al. [72], using RNAseq data from *H. vastatrix* in vitro structures (Figure 2), predicted the secretome of the prepenetration fungal structures. All together, these results generated a collection of 516 transcripts from *H. vastarix* that were predicted as putative secreted proteins. Surprisingly, a high number of these proteins were transcribed in prepenetration fungal structures, representing an early building of the pathogen's virulence machine.

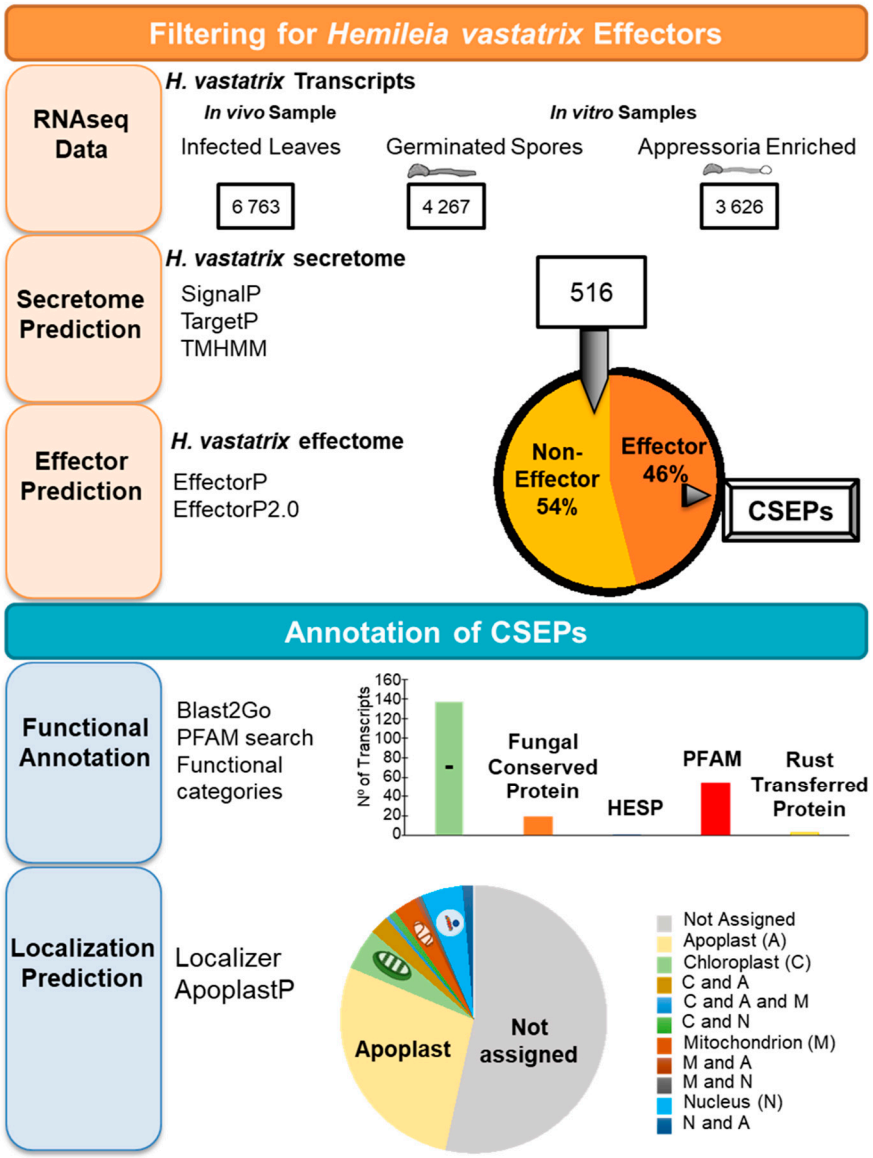

Figure 2. Pipeline for transcriptomic analysis of *Hemileia vastatrix* key differentiation stages, gene assembly, secretome prediction and bioinformatic annotation.

A machine learning approach was used to predict "Candidate secreted effector proteins" (CSEPs) from *H. vastatrix* secretome [73,74] (Figure 2). Almost half of the predicted secretome (516 transcripts) were also predicted to be CSEPs. In parallel, in silico annotation, such as the protein families database (Pfam) search, or functional annotation of those CSEPs sequences, revealed that 137 sequences do not contain any conserved protein domain. The activation of genes encoding putative effectors, namely the early activation of RTP (rust transferred proteins) and Gas1-orthologous genes, was observed in susceptible genotypes. Other putative effectors, (e.g., HESP—haustoria expressed secreted protein) seem to be specifically activated in the resistant genotypes and are preferentially expressed after the differentiation of the first haustoria [75,76]. The *H. vastatrix* CSEPs predicted subcellular localizations were apoplastic space (28%), nucleus (5%), chloroplast (5%), and mitochondrion (3%). However, for more than half of the CSEPs no localization was assigned (Figure 2).

The MEME algorithm was used to search for new conserved motifs amongst the sequences obtained by Fernandez et al. [71] and Talhinhas et al. [72]. Four putative secreted proteins were selected [77] (Figure 2) that shared some common features, such as gene organization and amino acid patterns, and their transcript level peaked seven days after inoculation in infected coffee leaves, when haustoria were the predominant fungal

structure present. Together these results suggest a similar biological function or a common ancestor. The CSEPs were immunolocalized inside of intercellular hyphae and haustoria of *H. vastatrix* in infected leaves. The selected sequences showed the hallmark of true effectors, which needs to be supported by the ongoing effort of identifying the plant proteins interactors. Surprisingly, two CSEPs revealed splicing variants, which had a distinct transcription profile in leaves of *Coffea* spp. inoculated with different *H. vastatrix* isolates, and a different subcellular localization in leaves of *Nicotiana benthamiana* agroinfiltrated with the different variants. The splicing variants identified may contribute to increasing the "arsenal" diversity that *H. vastatrix* employs in the "arms race" against *Coffea* spp. immunity and may contribute to the diversification of *H. vastatrix* virulence potential [77].

The first CSEP from *H. vastatrix* to be identified as a *bona fide* effector was described in a noteworthy study conducted by Maia et al. [78] that started with the identification of CSEPs using RNAseq data. The novelty presented in this publication lies in the system used to deliver CSEPs into the cytoplasm of coffee leaf cells: the type-three secretion system of *Pseudomonas syringae* pv. *garcae*. Once proved that the CSEPs were inside the cells, the authors could determine which CSEPs influenced the growth of *P. syringae* pv. *garcae* in selected *Coffea* genotypes. They observed a suppression of bacterial growth by HVEC-016 effector, when inside of leaves from S_H1 plants; suggesting that this effector can be recognized by a coffee plant with a S_H1 background. This tool for delivering CSEPs inside leaf cells is of special relevance for further studies, considering the reduced number of molecular tools available for functional characterization in coffee plants.

5. Disease Resistance Breeding

Disease resistance is often the most dynamic component of the crop breeding process, requiring continual updating due to pathogen adaptation to plant genotypes [79]. It is challenging to breed varieties with resistance that is effective, stable and broad-spectrum.

Plant disease resistance can be categorised in several concepts that are related to different aspects, including the genetic background of the resistance (monogenic/polygenic), the effect of the measurable phenotypic response (complete/partial resistance) and the effective broad-range or species-specific nature of resistance against pathogens (race-specific and race nonspecific resistance) [39].

For many years, selection for *H. vastatrix* resistance has been based on highly specific complete resistance derived from major introgressed genes derived from *C. arabica* (S_H1, S_H2, S_H4 and S_H5), as well as diploid species such as *C. canephora* (S_H6–S_H9) or *C. liberica* (S_H3) [11,19,20]. However, the pathogen's high degree of variability and adaptability, together with the consequent occurrence of frequent shifts in pathotypes, has resulted in the gradual loss of the resistance based on major S_H genes. Partial and non-specific polygenic resistance to *H. vastatrix* had been identified in *C. canephora*, in some *C. arabica* genotypes and interspecific hybrids [52,80,81] and had been associated with the slow epidemic progress and less defoliation [82]. Thus, coffee breeding programs are trying to develop strategies to improve the durability of CLR resistance in Arabica cultivars, namely through the combination of specific (complete) and nonspecific (partial) resistance [80,83].

Molecular marker-assisted selection (MAS) offers the chance to speed up individual resistance screening and increase breeding efficiency, allowing gene stacking into a single line with a high degree of parental genome recovery. In fact, current developments in plant breeding are moving towards combining different forms of resistance simultaneously by pyramiding various genes that cover a diverse range of resistance mechanisms. As promising as these strategies are for durable broad-spectrum resistance, they require the tagging of resistance genes by tightly linked markers, and ultimately their molecular characterization, which can be a hard task when dealing with highly complex polygenic traits in polyploid species. To date, the S_H3 locus derived from *C. liberica* has been the only rust-resistance gene genetically and physically characterized in coffee [84], corresponding to a complex multi-gene cluster which includes at least three R-genes (i.e., CC-NBS-LRR type) [85]. Despite these constraints, over the last seventeen years a few studies have

successfully developed markers closely linked to some *H. vastatrix* resistance genes in *C. arabica* and HDT-derivatives. Prakash et al. [86] and Mahé et al. [87] developed the first locus-specific markers cosegregating with S_H3 derived from introgression into *C. arabica*. Herrera et al. [80] followed by identifying AFLP and SSR markers associated with partial rust resistance in an HDT-derived population, and later Romero et al. [88], analyzing the same population, mapped a quantitative trait locus (QTL) associated with a new SH factor only present in genotypes derived from CIFC 1343 and H832/2 accessions. Using an F2 population of an HDT-derived line, de Brito et al. [89] identified a genomic region involved in resistance to race II, suggesting it corresponds with one of the S_H genes (S_H7–S_H9) present in HDT or another unknown gene, for which Diola et al. [90] developed SCAR markers flanking it. More recently, resistance to three different *H. vastatrix* pathotypes in another HDT-derived lineage was shown to be conferred by at least two independent dominant QTLs [91]. These genetic resources opened new possibilities for MAS-driven resistance breeding in coffee, prompting the first reports of successful marker validation and selection of coffee cultivars harboring distinct loci for resistance, not only to CLR, but also to coffee berry disease (CBD) [92,93]. Other promising genomic-driven approaches to improve coffee breeding for durable and broad-spectrum resistance have been studied, such as genomic selection [94], and genomics-assisted exploitation of mutant or impaired susceptibility (S)-genes in the host plant that will lead to "loss of susceptibility" [95].

5.1. Sources of Resistance to CLR

Coffee breeding for CLR resistance emerged at the turn of the 20th century through the work of enterprising growers aiming to obtain Arabica cultivars with improved resistance to *H. vastatrix*. The first such breeding endeavor was conducted in 1901, in Indonesia, with materials derived from several spontaneous interspecific hybrids between *C. arabica* and *C. liberica*, but without success, and soon the work was abandoned [53]. Afterwards, the first results of early selection efforts to obtain Arabica host resistance to CLR were reported in India around the 1920s, and although having a long history of initial successes, they were followed by disappointments, namely of the folk selections "Coorgs" and "Kents", which quickly fell susceptible to the disease [54].

Between 1925 and 1926 the Experimental Station of Balehonnur, in India, started a genetic breeding Arabica program for resistance to *H. vastatrix* based on interspecific hybrids resulting from crosses carried out by regional coffee growers between plants of the local variety of *C arabica* and plants of *C. liberica* species. The earliest of such hybrids involved in Arabica breeding was S.26 carrying the S_H3 gene, which was introduced in the development of the Indian coffee selections S.288 and S.795 and released for commercial cultivation in late 1930s. These coffee selections, which initially showed resistance to *H. vastatrix* in the field, began, after some years of cultivation in India, to be affected, though without great severity [96,97]. From 1952 onwards, several sources of resistance in *C. arabica* were identified and classified in CIFC into eight physiological resistance groups (C, α, D, J, ϒ, I, W and L) in coffee trees originating from Ethiopia and Sudan, some of which received designations known today such as Dilla & Alghe, Geisha, Barbuck Sudan, BE-5 Wush Wush, S4 Agaro, S.6 Cioiccie, S.12 Kaffa and S.16 Wollamo. However, none of these coffee trees showed resistance to all known rust races [11,20].

Contrary to what was seen with *C. arabica*, it was quite easy to find plants with high resistance to the races of *H. vastatrix* within diploid species such as *C. canephora*, *C. congensis*, *C. dewevrei* and *C. liberica*, and others [98]. In an attempt to introduce such resistance into *C. arabica*, researchers of Brazil and Ivory Coast developed tetraploid *C. canephora* trees with resistance to *H. vastatrix* through colchicine duplication of the chromosome number of the coffee plants, which in turn were hybridized with traditional cultivars of *C. arabica*, giving rise to the Icatú varieties in Brazil in 1950 and Arabusta in Ivory Coast in 1960 [11,99–101]

5.1.1. Spontaneous Interspecific Hybrids

The occurrence and discovery of spontaneous interspecific coffee hybrids over the last two centuries has provided important sources of rust resistance. From 1886 onwards, numerous spontaneous hybrids showing resistance to *H. vastatrix* were found in various coffee-growing regions, such as the hybrids of *C. arabica* × *C. liberica* designated as "Kallimas", "Bandjar Sari" and "Kawisari B and D" in Indonesia [53]. In the early 50's, the hybrid Devamachy (*C. arabica* × *C. canephora*) was found in India, being still commercially exploited as "Selection-5" [102], while the most recent evidence for spontaneous hybridization of *C. arabica* and *C. canephora* has come from New Caledonia [103]. Nonetheless the contribution of these hybrids for improving coffee resistance, the greatest discovery to date of a natural hybrid widely impacting on coffee production, was that of the HDT, which led to a turning point in coffee breeding history.

5.1.2. Timor Hybrid (HDT)

In 1927, in a plantation of the Arabica's variety Typica on the Timor island (East Timor was a Portuguese colony), a coffee tree showing no disease symptoms within a highly rust affected field was discovered, resulting from a natural cross between *C. arabica* and *C. canephora* [104–106]. Seeds from this plant were used to establish small coffee plantations, giving rise to a population, commonly known as "Timor hybrid", which presented a phenotype similar to Arabica and a marked resistance to *H. vastatrix*. Seeds from the best plants of this population were used from 1956 onwards for the formation, on a large scale, of new coffee plantations throughout the island. Following this expansion, in the 1960s, about 60% of the coffee cultivated in Timor-Leste was Arabica, of which 80% consisted of the CLR-resistant HDT variety [104,107]. Within its mission of supporting coffee breeding worldwide, CIFC received numerous HDT samples from East Timor, from which the most used as sources of resistance in breeding programs, as well as in genetic studies, are: CIFC HDT 832 (received 1957); CIFC HDT 1343 (received 1960); CIFC HDT 2570 (received 1968) and the clone CIFC HDT 4106 (1971) from the supposed original hybrid of Timor [60]. From the studies, one of the major breakthroughs for the Arabica coffee breeding programs was the discovery of the resistance factors of HDT, as well as the possibility to transfer these characteristics to the traditional commercial varieties [7,11]. Based on those HDT resources, during the second half of the 20th century comprehensive breeding programs applying Mendelian and quantitative genetics, plant pathology, crop physiology and agronomy, were implemented by research centers in several coffee growing countries: India (CCRI), Brazil (IAC, IAPAR, UFV-EPAMIG, PROCAFÉ/MAPA), Colombia (CENICAFE), Costa Rica (CATIE/PROMECAFE/CIRAD), Kenya (CRF), Tanzania (TaCRI) and Angola/Portugal (IAA/ICA-CIFC/ex IICT) [6,100,108].

5.1.3. HDT Germplasm

From the originally received HDT genotypes channeled by CIFC for several countries, an explosive production of rust resistant germplasm followed in the scope of local Arabica breeding programs. For instance, HDT 832/1 was the progenitor for development of varieties such as Sabiá, Palma, Oeiras, Canário and Liberdade in Brazil; Anacafe 14, Catisic, Fronton, Oro Azteca Catimor, Costa Rica 95, Ihcafe 90, Lempira in Central America and Cauvery in India [100,109–111]. HDT 832/2, on the other hand, was the progenitor for the development of varieties Acauã, Tupi, Obatã, Iapar 59, IPR 98, IPR 99, IPR 104, Arara, Asa Branca in Brasil [109,110,112] and Chandragiri in India [113], Cuscatleco, Limani, Marsellesa, Parainema, Milenio as well as F1 Hybrids Starmaya and Mundo Maya (T5296 × wild Ethiopian accessions) in Central America [111,114,115]. Using a multilineal strategy of compound varieties, CIFC HDT 1343 was extensively used in Colombia to produce, among others, Colombia, Tabi, Castillo and Cenicafé 1 [116–118]. CIFC HDT 1343 was also used in Kenya to develop the varieties Ruiru 11 and Batian, as well as cultivar Catimor 129 grown in several African growing countries such as Malawi and

Zimbabwe [111,119,120]. Finally, the introduction in Brazil of CIFC HDT 2570 gave origin to the varieties Araponga, Paraíso, Catiguá and Pau Brasil [110,121].

CIFC had also a major role in selecting from HDT populations genotypes with different levels of resistance to *H. vastatrix*, and the majority were sent to research institutions in different coffee regions in the world. In some of these regions, such as Brazil, some populations descending from HDT received widely referenced designations such as Catimor and Sarchimor [11,100,122]. The populations derived from the hybrids CIFC HW 26 (19/1 Red Caturra × HDT 832/1) and CIFC HW 46 (19/1 Red Caturra × HDT 832/2) received at UFV the designation of Catimor, resulting from the contraction of the words Caturra and HDT [123]. Later, the same designation of Catimor came to be used in several different contexts, such as derivatives of the Hybrid" Yellow Catuaí CCC 135 × HDT 1343" produced by CENICAFÉ in Colombia. Since the 1980s, the name Catimor has been indiscriminately used by researchers, breeders, and roasters to designate varieties, cultivars, introductions, "accessions" and different genotypes derived from hybrids between Arabica (Caturra and Catuaí) and any HDT introduction. On the other hand, populations originated from the hybrid CIFC H 361 (Villa Sarchi CIFC 971/10 × CIFC 832/2) received the designation of Sarchimor, analogous with the name Catimor. Other designations have been attributed following the same rationale. The cross between Yellow Caturra CIFC 1637 and CIFC H361/4 gave rise to the hybrid CIFC H529, which in Brazil received the designation UFV 351 and originated the genetic material that later came to be generically designated as Cachimor [124–126].

In recent years, in some coffee-growing countries, some resistant varieties have shown susceptibility to rust [7,60,112]. The same happened to the original sources of resistance HDT 832/1, HDT 832/2 and the clone of the supposed original HDT hybrid, CIFC 4016, that showed susceptibility to rust samples from some coffee growing regions under greenhouse conditions at CIFC [60]. However, in many countries, although some resistant varieties started to show some susceptibility, they are still preferred for their agronomic characteristics when compared to traditional varieties once the basic condition of productivity of these coffee trees persists [60,112,127].

Many HDT derivatives offer resistance, not only to coffee leaf rust, but also to root-knot nematodes (*Meloidogyne* spp.), coffee berry disease (*Colletotrichum kahawae*), bacterial blight of coffee (*Pseudomonas syringae* pv. *garcae*) and possibly other pathogens [119,121,128–133].

6. Coffee Defense Mechanisms

Significant advances have been made in the knowledge of the resistance mechanisms induced by the pathogen at the cytological and biochemical levels and, more recently, through analytical chemistry, gene expression analysis and the application of various omics approaches (as summarized in Tables 1–3). Nevertheless, the existence of constitutive barriers in coffee that could prevent *H. vastatrix* infection has not been disclosed so far [52,134,135]. Cytological studies revealed that once *H. vastatrix* urediniospores germinate, germ tubes generally have a similar level of success in finding stomata and forming appressoria in resistant and susceptible coffee leaves [52,136]. However, in resistant plants, fungal growth is typically arrested in any of the sequential stages of appressorium, penetration hypha, anchor or haustorial mother cell, with or without haustorium. Therefore, two types of resistance can be characterized: (i) pre-haustorial resistance, when the fungal growth stopped before haustorium formation in the majority of the infection sites; (ii) post-haustorial resistance, when the fungus growth stopped more frequently after forming at least one haustorium [52,136–142]. Both types of resistance are associated with the HR, although this response is displayed earlier in the pre-haustorial than in the post-haustorial resistance. HR is first observed in the guard cells only, or in both the guard and subsidiary stomatal cells, at infection sites in which the fungus ceased its growth in the stage of appressorium or in the subsequent pre-haustorial structures. HR of subsidiary and mesophyll cells invaded by haustoria is observed later and, during the time course of infection, cell death spreads to adjacent noninvaded cells [52,136,137,140–142].

Table 1. Coffee defense responses induced by *Hemileia vastatrix*, based on different research fields: cytology, analytical chemistry, and biochemistry.

Research Fields	Coffee Defense Responses	References
Cytology	ROS accumulation in the cell walls and cytoplasmic contents	[136,143,144]
	Deployment of hypersensitive response (HR)	[52,136,137,140–142]
	Accumulation of phenolic-like compounds (Cell walls and cytoplasmic contents)	[52,136,137,140]
	Lignification of cell walls	[52,137]
	Haustorium encasement with callose and β-1,4-glucans	[52,137]
	Cell hypertrophy	[20,52,137]
	Accumulation of a material partially crystallised (containing pectins, polysaccharides and phenolic-like compounds) in the intercellular spaces	[52,137]
Analytical chemistry	Increase in salicylic acid (SA) levels	[145]
	Increase of chlorogenic acids (4,5-diCQA) content	[146]
	Increase in chitinases and glucanases activity	[147,148]
	Immunodetection of class I chitinases	[147]
Biochemistry	Increase in peroxidase (POD) activity	[136]
	Increase in superoxide dismutase (SOD) activity	[139]
	Increase in lipoxygenase (LOX) activity	[149]
	Increase in phenylalanine ammonia lyase (PAL) activity	[137]

Table 2. Genes putatively involved in coffee resistance to *Hemileia vastatrix* based on RT-qPCR analysis.

Gene	Annotation	Accession Number	Reference
CaRLK	Receptor-like kinase	DSS6; CF589181	[140,150]
NB-ARC domain	NB-ARC domain-containing disease resistance protein	n.a.	[151]
SD1-8	Receptor-like serine/threonine-protein kinase SD1-8	n.a.	[151]
NBS-LRR	Nucleotide-binding site–leucine-rich repeat	DQ123968; GT030058.1	[152,153]
At5g39020	Putative probable receptor-like protein kinase At5g39020	n.a.	[151]
LRR_RLK2	Leucine-rich repeat receptor-like protein kinase	Contig_37_g342.t1	[22]
RGH1A	Resistance gene analogs 1A	GT029983.1	[152]
NDR1	Non-race specific Disease Resistance 1	DSS12; CO773976	[138,150,154]
CDPK5	Calcium-dependent protein kinase 5	GT030068.1	[152]
CBP	Calmodulin-binding protein	GT030070.1	[152]
CaWRKY1	WRKY transcription factor 1	DSS16	[138,140,150,155,156]
CaWRKY1a	WRKY transcription factor 1a	n.a.	[156,157]
CaWRKY1b	WRKY transcription factor 1b	n.a.	[156,157]

Table 2. *Cont.*

Gene	Annotation	Accession Number	Reference
CaWRKY3	WRKY transcription factor 3	GT715378; GT715379; GT669686; GT684003; GT675420; GT675421; GT675422; GT675423	[155]
CaWRKY6	WRKY transcription factor 6	GW460548; GW439927; GT671542; GT700942; GT688469; GT722306	[155]
CaWRKY7	WRKY transcription factor 7	n.a.	[155]
CaWRKY8	WRKY transcription factor 8	GT685360; GW436389	[155]
CaWRKY10	WRKY transcription factor 10	DV693086	[155]
CaWRKY11	WRKY transcription factor 11	GW489409; GW472658; GW489686; GW467855	[155]
CaWRKY12	WRKY transcription factor 12	GW487300; GT715908	[155]
CaWRKY13	WRKY transcription factor 13	GW428837; GW469454	[155]
CaWRKY14	WRKY transcription factor 14	GT730216; GT688262; GT688263; GT733537	[155]
CaWRKY15	WRKY transcription factor 15	GT725660; GT721476; GT721477; GT704531; GT707389; GT702040; GT702041; GW490838; GT695761; GT674787; GT704614	[155]
CaWRKY17	WRKY transcription factor 17	DV678740	[155]
CaWRKY19	WRKY transcription factor 19	GW490173; GW439047; GW438774; GW472647; GW481654	[155]
CaWRKY20	WRKY transcription factor 20	DV706804	[155]
CaWRKY21	WRKY transcription factor 21	DV709595.1	[155]
CaWRKY22	WRKY transcription factor 22	GT685546; GT684702	[155]
bHLH	Putative basic helix-loop-helix (bHLH) DNA-binding superfamily protein	n.a.	[151]
AP2-type transcription factor	AP2-type transcription factor	DSS17	[150]
bZIP56	Transcription factor bZIP56	GT030080.1	[152]
MAPK2	Mitogen-activated protein kinase 2	GT030062.1	[152]
MEK2	Dual specificity mitogen-activated protein kinase kinase 2	GT030000.1	[152]
13-LOX	Lipoxygenase 13	DV704189	[140,142]
LOX	Lipoxygenase	DQ123948	[153]
CaPAL	Phenylalanine ammonia lyase	DQ067599; JF838179	[140]
NPR1	Non-expressor of pathogenesis-related gene	n.a.	[154]
CaGT	Salicylic acid-glucosyltransferase	DSS22; CO773975	[140,150]
ERF	Ethylene-responsive transcription factor 1B	n.a.	[151]
ABC	PDR-type ABC transporter 1	DQ123937	[153]
PR1	Pathogenesis-related protein 1	n.a.	[154]

Table 2. *Cont.*

Gene	Annotation	Accession Number	Reference
CaPR1b	Pathogenesis-related protein 1b	DQ335594	[140,142,143]
PR2	Pathogenesis-related protein 2 (beta-1,3-glucanase)	DQ123927	[153]
PR5	Pathogen-related protein 5 (thaumatin-like gene)	GT030025.1	[152]
CaPR10	Pathogenesis-related protein 10	CF589103	[140,143]
PNC2	Cationic peroxidase 2	n.a.	[151]
R1A-6	Putative late blight resistance protein homolog R1A-6	n.a.	[151]
RGA1	Putative disease resistance protein RGA1	n.a.	[151]
PUB24	Putative E3 ubiquitin-protein ligase PUB24	n.a.	[151]
ITN1	Putative ankyrin repeat-containing protein At3g12360	n.a.	[151]
Dirigent-like protein	Putative disease resistance-responsive (dirigent- like protein) family protein	n.a.	[151]
Premnaspiridione oxygenase	Premnaspiridione oxygenase	n.a.	[151]
CyP450	Cytochrome P450	DSS10	[150]
HSP70	70-kDa heat shock proteins	DSS11; DSS16; CO773974; DQ335599	[150]
CaR111	Unknown function	DSS23; CF589193	[138,150]

n.a.—not available.

Table 3. Coffee leaf apoplastic proteins that increase in abundance in the resistant plants at 1, 2, 3 and 4 days after inoculation (d.a.i.) with *H. vastatrix* (based on [141]).

d.a.i	Protein Identity [a]	Superfamily [b]	Functional Annotation [c]	Number of Spots
1	Calcineurin-like phosphoesterase	Metallophosphatases	Miscellaneous enzymes	1
	Cysteine proteinase aleuran type	Peptidase_C1	Protein degradation	1
	Subtilisin-like protease	Peptidases_S8_S54	Protein degradation	2
	Berberine bridge enzyme	FAD_binding	Secondary metabolism	1
	Osmotin	GH64-Thaumatin-like	Stress/Defense	1
	Cysteine-rich repeat secretory protein 55-like	Stress-antifungal	Stress/Defense	1
	Chitinase-like protein	GH18_chitinase-like	Stress/Defense	1
2	Chitinase-like protein	GH18_chitinase-like	Stress/Defense	2
	Beta-xylosidase/alpha-L-Arabinofuranosidase	GH3	Cell wall degradation	7
	Pectin methylesterase	Pectinesterase	Cell wall	1
	Pectinesterase-like	Pectinesterase	Cell wall	1
	purple acid phosphatase	Metallophosphatases	Miscellaneous enzymes	1
3	Aspartic proteinase nepenthesin-1-like	pepsin_retropepsin	Protein degradation	2
	Serine carboxypeptidase	Peptidase_S10	Protein degradation	4
	Subtilisin-like protease	Peptidases_S8_S53	Protein degradation	6
	Chitinase-like protein	GH18_chitinase-like	Stress/Defense	1
	Pathogenesis-related protein 5-like	GH64-Thaumatin-like	Stress/Defense	1

Table 3. *Cont.*

d.a.i	Protein Identity [a]	Superfamily [b]	Functional Annotation [c]	Number of Spots
4	Beta-xylosidase/alpha-L-Arabinofuranosidase	GH3	Cell wall degradation	1
	Alpha-L-fucosidase	Alpha-amylase	Cell wall degradation	2
	Non-cell-autonomous protein pathway	Aldose_epim	Minor CHO metabolism	1
	Lysosomal alpha-mannosidase-like	GH38	Miscellaneous enzymes	2
	Alpha-xylosidase 1	GH31	Miscellaneous enzymes	1
	ASPARTIC PROTEASE IN GUARD CELL-like protein	pepsin_retropepsin	Protein degradation	2
	Germin-like protein	Cupin	Stress/Defense	1

[a] The peptides separated by 2-DE were identified by matrix assisted laser desorption/ionization time of flight-mass spectrometry (MALDI—TOF/TOF MS) followed by homology search on NCBI Viridiplantae and ESTcoffee databases; [b] Superfamily according to NCBI classification. GH—Glycoside Hydrolase; FAD_binding—flavodoxin binding oxidoreductase; [c] Functional annotation based on MapMan 'Bin' and Go ontology.

In susceptible coffee genotypes, fungal colonization results in sporulation. Nevertheless, there is a variable proportion of germinated urediniospores that fail to form haustoria and are associated with HR [136,137,141,142], suggesting the existence of basal resistance. Thus, in both compatible and incompatible coffee-*H. vastatrix* interactions it seems that the contact between the fungus and the host cells triggers PAMP induced responses and is sufficient to induce HR of stomatal cells. In the incompatible interactions, the HR of host cells invaded by haustoria can be attributed to ETI, as well as other host responses, that result in the arrest of fungal growth.

HR has been monitored by autofluorescence and/or browning of the cytoplasmic contents or by its deep blue staining with Evans's blue [52,136,137,140–142]. Ultrastructural modifications of coffee leaf cells undergoing HR reveal breakdown of membranes, change in the appearance of chloroplasts and the nucleus, and coagulation of the cytoplasm [136,137].

Most of the *C. arabica*–*H. vastatrix* incompatible interactions have been characterized as post-haustorial resistance [52,136,137,141,147]. Resistance-donor genotypes, such as the Kawisari hybrid (*C. arabica* × *C. liberica*), used in breeding programs in India, also have post-haustorial defense mechanisms [142], unlike some HDT derivatives used worldwide [60,140,151]. Particularly, HDT832/2 displayed similar pre-haustorial mechanisms in host resistance to *H. vastatrix* and nonhost resistance to *Uromyces vignae*, as revealed by light microscopy, RT-qPCR gene expression analysis [140] and 454 pyrosequencing [60], which may explain the longer durability of resistance found in this coffee genotype. Indeed, according to Niks et al. [158] and Vaz-Patto et al. [159], mechanisms of rust resistance acting before the haustoria formation, which are very common in nonhost interactions, is hard to overcome by the pathogen, and therefore is of practical interest for breeding.

Almost twenty years have passed since the first identification of *Coffea* spp. genes involved in the defense response to *H. vastatrix* [150]. Fast-forward to the present day, methodologies such as cDNA_AFLP sequencing [152], and several transcriptomic approaches as suppression subtractive hybridization (SSH) [150,153,160], 454 pyrosequencing [161], and high throughput RNA sequencing by Illumina [151] have been used to increase understanding of the coffee resistance mechanisms. These methodologies have allowed the identification of genes putatively involved in coffee resistance to *Hemileia vastatrix*, namely genes related to pathogen recognition, signaling, transcription, defense, oxidative burst, hypersensitive response, phytohormones pathways, synthesis and transport of antimicrobial proteins/metabolites, secondary metabolites biosynthesis, and callose deposition (Table S1).

Plant perception of the pathogen invasion follows a surveillance system assembled in a multilayer fashion to identify apoplastic and cytoplasmatic pathogen effectors. At the early stages of the infection process, some of the multi-domain recognition receptors are activated in the incompatible coffee-*H. vastatrix* interaction (*RLK* and *LRR-RLK2, NBS-LRR*), suggesting their role in the host resistance response [22,140,150,152,153]. Nevertheless, in some other incompatible coffee-*H. vastatrix* interactions, this may not be the case [143,152],

indicating that immune receptors can have different mechanisms for ligand binding and receptor complex formation, which can modulate the activation, intensity and duration of plant immune responses [162]. Non-race specific disease resistance 1 (NDR1), an important activation element of PTI and ETI defense barriers, is required to rapidly activate and amplify the initial events following pathogen perception [163]. *CaNDR1* encodes for a plasma membrane-resident protein with a similar structure to the NDR1/HIN1-like (NHL) protein superfamily of plant defense-associated proteins [164]. In different *C. arabica* genotypes, *NDR1* was found to be significantly up-regulated during HR [138,150,154], and its functional characterization in coffee plants predicts a similar mechanistic conservation as observed in *Arabidopsis* [164,165].

A rapid increase in cytoplasmic calcium concentration is one of the earliest defense responses in PAMP-induced immunity. Ca^{2+} is one of the most prominent secondary messengers, and its spatial distribution in the cell is controlled by a complex network of calcium sensors and channels that operates at the plasma membrane, cytosol and organelles, including the nucleus [166]. Ca^{2+} binds to a plethora of sensors such as, calmodulin (CaM), CaM-like proteins (CML), and calcium-dependent protein kinases (CDPK) that activate target proteins either by direct binding or through phosphorylation (P) [167]. Two calcium-related genes (Calcium-dependent protein kinase 5—*CDPK5*, and Calmodulin-binding protein—*CaMBP*) have been studied and related to coffee resistance to rust [152]. The accumulation of calcineurin-like phosphoesterase (a calcium-dependent phosphatase) in the apoplast of resistant coffee leaves, was shown by proteomic analysis [141], emphasizing the importance of this molecule (together with phosphatases) in signal transduction and rapid defense response.

In addition to RLK and CDPK, mitogen-activated protein kinase (MAPK) is also involved to coffee resistance to *H. vastatrix*. MAPKs cascades play an essential role in transduction of environmental and developmental signals [168]. MAPKs are located in the cytoplasm or nucleus, and kinase cascades are activated by PAMPs or pathogen effectors [168,169]. The number of MAPKs involved in coffee resistance to *H. vastatrix* are still unknown. Diola et al. [152] identified three MAPKs, and only two (*MAPK2* and *MEK2*) were up-regulated in resistant *Coffea* spp. genotypes to *H. vastatrix* race II, suggesting that they are important signaling elements of the defense response.

One of the largest families of transcriptional regulators found exclusively in plants are the WRKY's. They were described as playing critical roles in repressing or activating plant defense responses through direct or indirect interaction with PAMPs, effector proteins or being regulated by MAPK [170,171]. According to Ramiro et al. [155] 22 unigenes encoding WRKYS transcription factors were identified in coffee. From these, 78% were activated in resistance responses to *H. vastatrix*. A first group of genes which included *CaWRKY6*, *CaWRKY11*, *CaWRKY12*, *CaWRKY13/14* and *CaWRKY15* was moderately activated while another set, *CaWRKY1*, *CcWRKY17*, *CaWRKY19/20/21*, was strongly and transiently activated during the time course of infection [150,155–157]. In coffee-*H. vastatrix* interactions, *CaWRKY1* (*CaWRKY1a* and *CaWRKY1b*) is one of the most studied WRKY genes and seems to be engaged in coffee resistance to *H. vastatrix*. Its early activation pattern is coincident with pathogen entry into the plant and deployment of HR [138,140,156,157]. Other transcription factors such as *Ap2* (AP2 type transcription factor) [150], *bHLH* (basic helix-loop-helix DNA- binding protein) [151] and *bZIP56* (bZIP transcription factor) [152] may also be involved in the regulation of resistance responses/defense mechanisms of coffee. These genes were found to be up-regulated in the several coffee-*H. vastatrix* incompatible interactions studied [150–152].

Phytohormones can regulate plant growth, developmental processes, and disease resistance. Among them, jasmonic acid (JA), salicylic acid (SA), and ethylene (ET) are classically related to plant defense acting interdependently through complex antagonistic or synergistic interactions [172]. Until now, the role and modulation of JA, SA and ET in coffee-*H. vastatrix* interactions lack a comprehensive study, but some clues have been disclosed by the expression profile of some phytohormone pathways-related genes. The regulation of

genes related to ethylene pathway (ACC oxidase—*CaACO1*, ethylene-responsive element binding factor 2—*CaERB2*, Ethylene-responsive transcription factor 1B—*CaERF*) and JA biosynthesis (allene oxide synthase—*CaAOS*, lipoxygenase—*Ca9-LOX* and *Ca13-LOX*) did not show clear evidence of the involvement of these phytohormones in the early coffee resistance responses to rust [140,142,151–153,155]. However, the activation of phenylalanine ammonia lyase (*PAL*), a SA biosynthesis gene and the non-expressor of pathogenesis-related gene (*NPR1*) a well-known SA-mediated protein–protein interactions, suggest that SA plays a key role in coffee defense to *H. vastatrix* [140,154,173]. Moreover, the simultaneous quantification of SA, JA and ABA in *C. arabica* leaves by LC/ESI-MS/MS showed an early increase in SA level in an incompatible interaction, while no significant variation was obtained for JA and ABA [145]. The pathogenesis-related proteins (PRs) genes, *CaPR1*, *CaPR2*, *CaPR5*, have also been associated with the induction of the SA pathway during the coffee immune response [140,142,143,152–154]. Up-regulation of *PR10* was also found in incompatible coffee-*H. vastatrix* interactions [140,143]. Most of the PR10 are intercellular proteins with RNase activity, which could provide protection to plants during HR in the infected area's surroundings, while directly inhibiting pathogen development [174]. However, PRs are relevant elements of the defense response machinery, many with antimicrobial functions, such as, PR2 (β-1,3-glucanase), PR3 (chitinases) and PR5 (thaumatin-like) [175,176]. An early increase of chitinase and glucanase activity in coffee-*H. vastatrix* incompatible interactions, but not in the compatible ones, was observed by Maxemiuc-Naccache et al. [148] using crude extracts of coffee leaves. Similar results were obtained when studying chitinase activity in intercellular fluids (IF), particularly the early increase in the cationic isoforms detected in the incompatible coffee-rust interactions. Immunodetection analyses performed with antibodies specific to class I chitinases revealed, again, the importance of these cationic isoforms in the incompatible interactions [147]. The proteomic analysis of the apoplastic coffee leaf proteins (which comprises cell wall and IF proteins) revealed that resistance was associated with an early increase of PR proteins, such as chitinases, thaumatin/osmotin, germin-like proteins (PR15 and PR16) and proteases (serine, cysteine and aspartic peptidases involved in protein degradation). Later, in the infection process the cell wall glycohydrolase (GHs) and other enzymes seem to play an important role in the coffee defense response (Table 3, Figure 3) [141]. Proteases, together with phosphatases, lead to a complex regulation of cell wall proteins through PTMs (post-translational modifications) that may affect PRR recognition and PR proteins with antifungal activity acting directly on pathogen inhibition/degradation. In addition, GHs confer great plasticity to cell wall polysaccharides, which in association with berberine bridge enzyme (reticulin oxidase –like), germin-like protein [oxalate oxidase or superoxide dismutase (SOD)-like] and other oxidative enzymes, can be involved in the cell wall cross-linking between phenolic compounds, polysaccharides and glycoproteins [141].

Oxidases have also been associated with the production of ROS via oxygen consumption in a so-called "oxidative burst" initiated in early defense reactions [177,178]. The oxidative burst involves a strictly controlled accumulation of ROS primarily composed of hydrogen peroxide (H_2O_2) and superoxide (O_2^-) in host cells following pathogen recognition [179,180]. Given its membrane permeability and affinity to several signaling molecules such as SA and nitric oxide (NO), the rapid production of ROS, such as H_2O_2, can act as secondary messengers in defense-related signaling pathways, providing additional regulatory functions in plant defense responses [179,180]. Whether ROS acts as a damaging or signaling molecule depends on the delicate equilibrium between ROS production and scavenging. In plants, major ROS-scavenging mechanisms include catalase, ascorbate peroxidases, and SOD enzymes [181]. The oxidative burst occurs as a biphasic ROS accumulation in plant-pathogen interactions. The first phase is an unspecific, low, and transient reaction occurring in both compatible and incompatible interaction. The second sustained phase with much higher magnitude depends on the recognition of the pathogen's *Avr* genes, assisting the establishment of disease resistance [39,180]. Based on light microscopic studies, Ramiro et al. [143] reported a biphasic accumulation of H_2O_2, which was detected

in a few stomatal cells from 15 hpi (hours post inoculation) and no differences were found between coffee-*H. vastatrix* incompatible and compatible interactions until 39 hpi. However, from this time point, intense DAB (3,3-diaminobenzidine) staining was observed in stomatal cells and adjacent epidermal cells of the coffee resistant genotype. Transmission electron microscope observations (following DAB treatments) revealed the localization of H_2O_2 in walls, middle lamellae, cytoplasmic contents and chloroplasts of stomatal coffee cells at the infection sites [136]. In addition to H_2O_2, the involvement of the superoxide anion radical O_2^- in HR was suggested by the significant inhibition of cell death after the treatment of coffee resistant leaves with ROS scavengers [144].

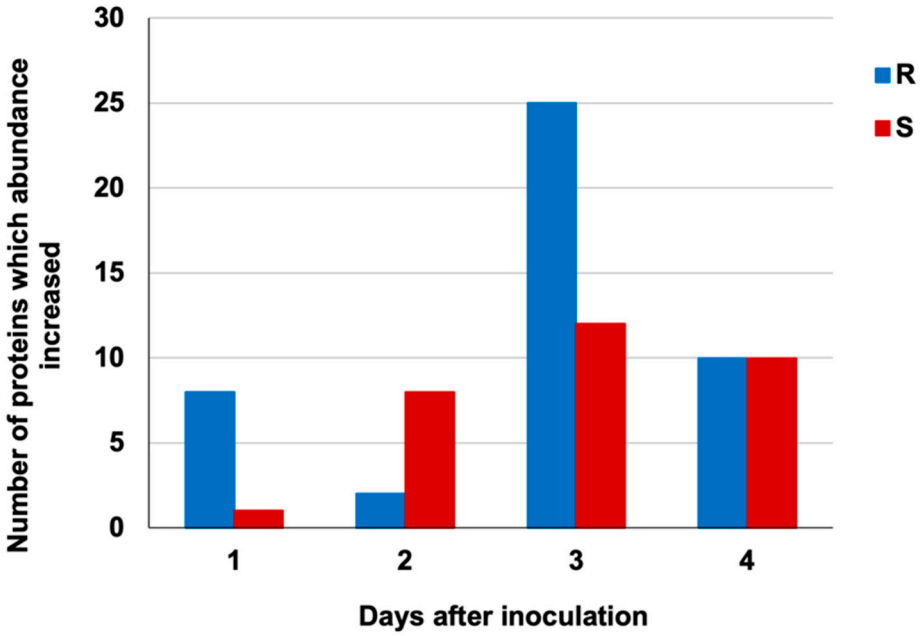

Figure 3. Number of leaf apoplastic proteins in which abundance increased in resistant (R) and susceptible (S) coffee samples obtained by proteomic analysis at 1, 2, 3, and 4 days after inoculation with *Hemileia vastatrix* [141]. Data show a biphasic increase in the number of proteins and a higher number of proteins changing in abundance in the resistance than in the susceptibility.

In some forms of HR, the rapid loss of cell membrane integrity is associated with ROS production and an increase in oxidizing enzymes, such as peroxidases and lipoxygenases (LOX) [36,177,182]. In incompatible coffee-*H. vastatrix* interactions, the induction of a cationic peroxidase gene (*PNC2*) was reported [151]. These observations are in line with the increase in POD activity of a new cationic isoform detected in isoelectric focusing gels [136]. Furthermore, the evaluation of the total POD activity in crude extracts revealed a peak of POD activity prior, or at the same time, as the beginning of HR in coffee-*H. vastatrix* incompatible interactions. A later increase of POD activity was also detected, being related to host cell wall lignification [136]. Additionally, the treatment of resistant coffee leaves with 2,4-dichlorophenol, an activator of peroxidases and other oxidases, resulted in a significant increase in cell death (HR). On the contrary, salicylhydroxamic acid, an inhibitor of the same enzymes and diphenyleneiodonium chloride, an inhibitor of NADPH oxidases, decreased cell death. These results suggest that the POD, NADPH oxidases, and eventually other oxidases, are involved in the HR of the coffee-rust interaction [136,144]. In an incompatible interaction a peak in total SOD activity was detected before cell death. The SOD isoenzymes pattern obtained by isoelectric focusing electrophoresis suggested that this could be attributed to isoenzymes with a pI between 4.7 and 5.4 [139]. In an incompatible coffee–rust interaction, LOX activity increased during the hypersensitive response. In contrast, the enzyme activity remained moderately constant in the compatible interaction [183]. LOXs catalyze the conversion of polyunsaturated fatty acids such as

linoleic acid into hydroperoxides, which may cause oxidative damage to plant membranes during the HR [149,184].

Plant phenolics are secondary metabolites consisting of structurally diverse compounds arising from shikimate–phenylpropanoid pathways. Several studies suggest that they are strongly involved in plant–pathogen interactions and may restrict the spread of a pathogen [185]. PAL is a key enzyme of the phenylpropanoid pathway that catalyzes the deamination of phenylalanine to trans-cinnamic acid, a precursor for SA, lignin and flavonoid biosynthetic pathways [186]. Lignin is a major phenolic polymer present in the secondary cell wall of vascular plants, and in addition to its roles in growth and development, it has been suggested to be a physical barrier against pathogens [187]. In coffee plants resistant to *H. vastatrix,* PAL activity revealed two peaks; one detected two days after inoculation, coincident with an early accumulation of phenolic-like compounds in the cell walls and cytoplasm, and the beginning of HR. A second peak was observed 5 days after inoculation that could be related to a later accumulation of phenolic compounds, and the host cell wall lignification, as confirmed by the phloroglucinol-HCl test [52,137]. Indeed, the quantification of chlorogenic acids (CGAs) performed by HPLC-DAD and LC-MS, which are also products of phenylpropanoid metabolism, was abundantly identified in coffee [188]. An early and significant increase of CGAs content, particularly 4,5-diCQA (4,5-dicaffeoylquinic acid), was observed in an incompatible *C. arabica-H. vastatrix* interaction comparatively to the compatible one and the control (healthy leaves) [189].

Haustoria encasement is another early host response observed in coffee-*H. vastatrix*-incompatible interactions. However, this response is also observed in compatible interactions, but later on, from the seventh day after inoculation, and in a small number of haustoria [52,137,142]. Cyto- and immunocytochemical studies revealed that haustoria are encased by material that reacted positively for callose and for β-1,4-glucans. Pectins are also localized around the penetration pegs, but not around haustorial bodies [51,137]. Encasement might have a role in plant defense by serving as a barrier to block effective uptake of host nutrients through haustoria and inhibiting the pathogen's effector delivery [146,190].

At advanced stages of the infection (around 5–7 days after the inoculation), transmission electron microscope observations of samples from *C. arabica* and *C. congensis* resistant plants [137] showed an intriguing accumulation of partially crystallised material in the intercellular spaces around the senescent hyphae, next to dead host cells and in close association with the middle lamella. That material was never detected in healthy or susceptible tissues. Cyto and immunocytochemical tests showed that at the beginning of accumulation, that material contained weakly esterified pectins. That material was also composed of polysaccharides as judged by PATAg test and phenolic-like compounds, as evidenced by autofluorescence. Cellulose, hemicellulose, HRGPs, and proteins were not detected. Although the role of this material is unknown, it might be the result of plant cell death associated with the slowdown of tissue invasion by the pathogen [52,137].

Hypertrophy of the mesophyll cells at the infection sites is a cytological response observed in different coffee resistant genotypes, from 6 days after inoculation [20,52,137], suggesting the possible involvement of growth regulators. The first cells to increase in size are those subjacent to the sub-stomatal chamber, and later all the spongy cells become irregularly shaped and some of them with thicker walls. Their nuclei also increase in volume (1.5×) as do the nucleoli (2–3×). The palisade parenchyma does not show any morphological alterations. During the cell volume increasement, the fungal hyphae are apparently crushed between the cells [20]. Those bigger cells give rise to a localized tumefaction and corresponded macroscopically to the reaction type *flt* (small chlorotic flecks associated with punctiform tumefactions). This reaction type is also observed in nonhost species of the *Rubiaceae* family [as revised by 137].

Most of the described responses induced by *H. vastatrix* occur in incompatible and compatible interactions, but earlier and with greater magnitude during the resistance response, particularly in pre-haustorial resistance.

7. Systemic-Acquired Resistance (SAR) in Coffee

The best characterized type of induced resistance mechanism is systemic-acquired resistance [191]. As an integral part of SAR, priming is a plant physiological state able to raise the activation of stress-induced defense responses. It has no or minimal negative impact on the host plants' energy status since primed plants deploy their defense repertoire only during pathogen attack, and not in a constitutive manner [42].

The activation of SAR by the application of plant resistance inducers (PRIs) that mimic a pathogen infection results in a stronger and faster defense response when biotic and abiotic stresses occur. Different PRI treatments, either chemical agents, extracts from plants or microbes have been used [192].

In coffee plants, protection against coffee leaf rust was achieved by treatments with different PRIs such as yeast extract [193], *Bacillus thuringiensis* [194,195], exopolysaccharides from bacterial cells of *Xanthomonas campestris* [196], acibenzolar-S-methyl (ASM—salicylic acid functional analog belonging to the benzothiadiazole (BTH) family) [153,197], potassium silicate [198], phosphites [199] and formulations based on natural products [200–202]. In field trials some of these PRIs used alone, combined, or in association with fungicides can significantly reduce CLR incidence [199–201]. The cellular mechanisms behind PRIS's effect on coffee leaves were studied using different molecular approaches. The increase in the enzymatic activities of chitinase and β-1,3-glucanase was observed after ASM treatment of coffee plants cv. Mundo Novo [153]. De Nardi et al. [203] used microarray hybridization to study the effect of BTH on coffee leaves. A shift from housekeeping to defense metabolism was found in BTH-treated leaves, with an increase in pathogenesis-related protein, oxidative burst and in cell wall strengthening processes. The coffee genes associated with SAR against CLR identified by suppression subtractive hybridization after ASM treatment [153] were involved in the oxidative burst, hypersensitive response, synthesis of antimicrobial proteins, synthesis and transport of antimicrobial metabolites, signal perception and transduction, metabolism of lipids, regulated protein degradation and cell maintenance and development.

In coffee leaves treated with phosphites (inorganic salts of phosphorous acid), the induction of the expression of defense-related genes, such as peroxidase, catalase, β-1.3-glucanase and PAL, was reported [199]. Biochemical studies further confirmed the increase in the activity of antioxidant enzymes (ascorbate peroxidase, superoxide dismutase, catalase and polyphenol oxidase) [199,204] and the photosynthetic rates of treated leaves [204]. Recently, a physiological (leaf gas-exchange), biochemical (enzymatic) and proteomic study was undertaken. Coffee leaves were treated with Greenforce CuCa (formulation prepared with coffee industry by-products supplemented with calcium and copper salts), ASM and inoculated with *H. vastatrix* [202]. Both PRIs prepared the plant to resist CLR, but they induced different mechanisms upon pathogen infection. Greenforce CuCa treatment showed an increase in stomatal conductance and photosynthetic rate, and it further reinforced the redox homeostasis of the leaf, while ASM seemed to affect preferentially the secondary metabolism and stress-related proteins.

A protection strategy that takes advantage of the plant immune system by eliciting constitutive defenses could be an alternative solution (replacing the fungicide treatments) for more sustainable coffee production management [205].

8. Conclusions and Perspectives

This review summarizes the progress made to date in the research of coffee-*H. vastatrix* interactions from both the plant and pathogen viewpoints. Extensive inheritance studies performed in the sixties represented a crucial milestone by showing that coffee-*H. vastatrix* interactions follow the Flor's gene-for-gene model. Based on this model, more than 55 rust races have been identified so far, according to their virulence spectra, on a set of defined coffee differentials. Molecular diversity among rust isolates has been reported, although a link with their phenotypic diversity has not yet been established. Nevertheless, recent

efforts in *H. vastatrix* genomic research may provide candidate markers associated with specific rust races in the near future.

The integration of recent advances in "omics" (including genomics, transcriptomics, effectoromics, and proteomics) upheld by phenotyping assays can fasten the identification of putative *H. vastatrix* effectors and the characterization of their virulence/avirulence functions in coffee. Up to now, only one candidate effector has been functionally validated, mainly due to technical difficulties posed by both the pathogen and the host, which makes it necessary to use heterologous systems. Future challenges include the implementation of assays to study effector's functions and the identification of plant cognate resistance genes, which will result in a deeper understanding of plant-pathogen "cross-talks", and *H. vastatrix*'s effector biology and its importance in pathogenicity. Altogether, this knowledge will help unveil R genes with the potential to accelerate and improve screening for disease resistance in coffee breeding.

In the late 1950s, a breakthrough for controlling CLR by resistant varieties was the discovery of HDT genotypes with resistance to all known rust races. This source of resistance was used by all coffee breeding programs allowing the release of the majority of resistant varieties grown nowadays. However, the resistance of some of these varieties has been progressively overcome due to the emergence of more virulent rust races, highlighting the dynamic nature of the plant and pathogen co-evolution. Entering into what seems to be a new cycle in CLR resistance, the identification, and characterization of new sources of resistance is crucial to face also the emergent epidemic resurgence of this disease in Latin America and the Caribbean, which is considered a natural disaster in the tropics.

This review updates the knowledge on the complex multilayer defense mechanisms of coffee to *H. vastatrix*, based on detailed studies that have been instrumental to elucidate several processes using cytological, biochemical, analytical chemistry, gene expression analysis, and various omics tools (as summarized in Figure 4).

Coffee resistance is characterized by restricted fungal growth (pre- or post-haustorial resistance) associated with several plant responses: the hypersensitive response, accumulation of ROS, haustoria encasement with callose and β-1,4-glucans, deposition of phenolic-like compounds, cell wall lignification, intercellular accumulation of pectin-like material also composed of polysaccharides and phenolic compounds, and cell hypertrophy. Additionally, the increase in the activity of oxidative enzymes [e.g., peroxidases (POD), lipoxygenase (LOX), and superoxide dismutase SOD)], phenylalanine ammonia-lyase (PAL), β-1,3-glucanase, and chitinases have been also detected. The apoplastic coffee proteome analysis revealed proteases (subtilisin, cysteine-like, serine and aspartic-like), hydrolases, and oxidases associated with coffee resistance. Within this complex cascade of events occurring upon rust infection, the salicylic acid-dependent pathway seems to play a decisive role mediating the coffee resistance response. Genes putatively involved in pathogen recognition, signaling, and defense have been identified in coffee-*H. vastatrix* interactions, such as, receptor kinases, subtilisin-like protease, WRKY transcription factors, glucosyltransferases, phenylalanine ammonia-lyase, and PRs. Furthermore, similar coffee defense responses induced by *H. vastatrix* have been observed using plant resistance inducers. Interestingly, resistant and susceptible coffee genotypes share the same type of responses when infected by *H. vastatrix*. However, these are observed earlier and with greater magnitude during the resistance response, particularly in pre-haustorial resistance. In fact, in HDT genotypes used as resistance sources in breeding programs, such as HDT832/2, pre-haustorial resistance mechanisms, show longer durability.

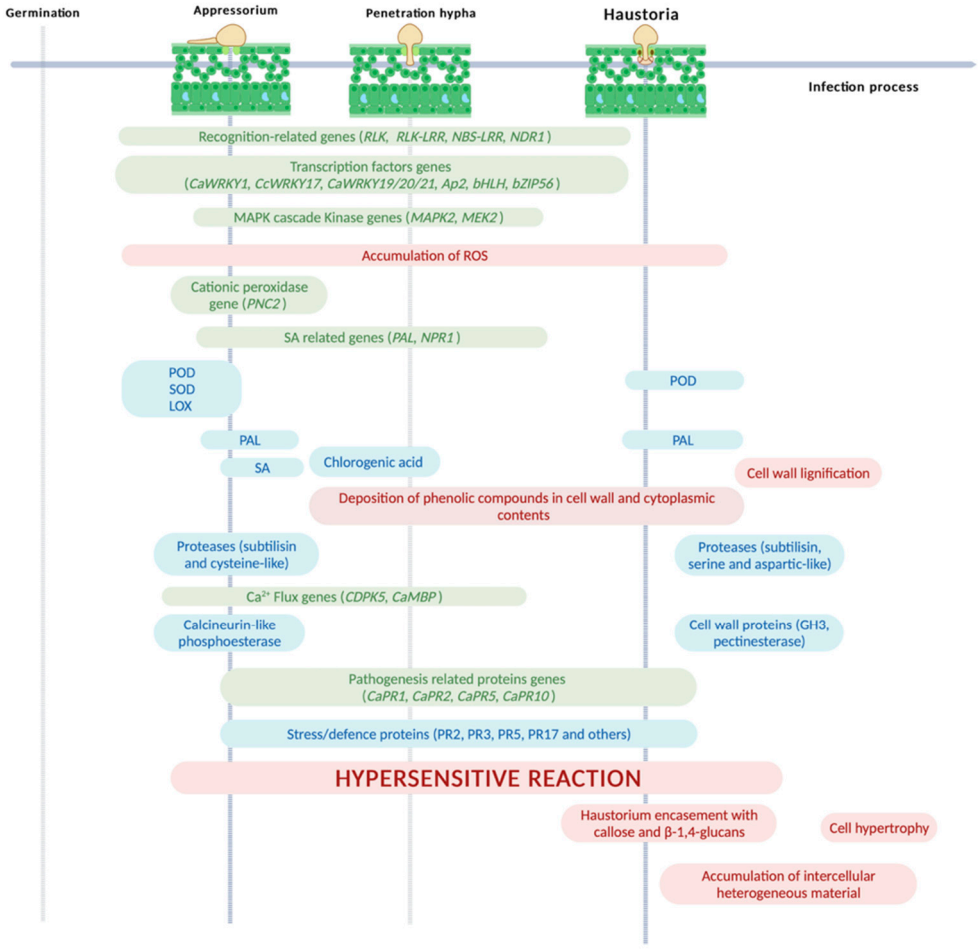

Figure 4. Schematic model of coffee defense responses of *Coffea* spp. to *Hemileia vastatrix*. The activation of genes, proteins and metabolites and cytological responses are indicated in green, blue and pink colors, respectively. RLK, receptor-like kinase; LRR-RLK, Leucine-rich repeat receptor-like kinase; NBS-LRR, nucleotide-binding site receptor-like kinase; NDR1, non-race specific disease resistance 1; WRKY's (WRKY1, WRKY17, WRKY19/20/21) WRKY transcription factor; Ap2, AP2 type transcription factor; bHLH, basic helix-loop-helix DNA- binding protein; bZIP56, bZIP transcription factor; MAPK2, mitogen-activated protein kinase 2; MEK2, mitogen-activated protein kinases 2; ROS, reactive oxygen species; PNC2, cationic peroxidase gene; PAL, phenylalanine ammonia lyase; NPR1, non-expressor of pathogenesis-related gene; POD, peroxidase; SOD, Superoxide dismutase, LOX, lipoxygenase; SA, Salicylic acid; GH3, glycoside hydrolase class 3; CDPK5, calcium-dependent protein kinase 5; CaMBP, calmodulin-binding protein; PR's (PR1, PR22, PR5, PR10) pathogenesis-related genes. Created with Biorender.com, access date 24 December 2021.

Although a better understanding of the cellular, biochemical, and molecular mechanisms of host resistance has been achieved, hard work still lies ahead for the research community working on coffee resistance, regarding a deep lack of information on resistance genes at all levels from identification and function to regulation. Given the current availability of genomic and EST data, candidate genes potentially involved in coffee-pathogen interactions have been identified, and it is expected that these resources will provide the opportunity to increase their number in a near future, allowing subsequent studies at the functional genomics level. Deep-sequencing has led to the discovery of several hundred small non-coding RNA (sRNA, miRNAs) involved in gene regulation, such as those required for immunity (R-genes). Although only recently, miRNA analyses in *C. arabica*-*H. vastatrix* interactions began to be unveiled [206], some miRNA families were identified as putative candidates for the mediation of coffee resistance and susceptibility, for which

putative targets were predicted but not yet validated. The characterization of miRNAs may shed light on the mechanisms that drive coffee resistance and susceptibility to CLR.

Regardless of all the significant advances obtained so far, in-depth research on coffee-*H. vastatrix* interactions driven by new advanced technologies is still crucial for developing efficient disease resistance breeding and new strategies for crop protection. As new and more powerful genomic resources become available, we have the opportunity to not only decipher the complexity of resistance processes, but also to revisit hypotheses previously generated.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/agronomy12020326/s1. Table S1: All genes putatively involved in coffee interaction to *Hemileia vastatrix* based on RT-qPCR analysis.

Author Contributions: Conceptualization, M.d.C.S.; writing—original draft preparation, M.d.C.S., L.G.-G., I.D., A.L., H.A., A.P.P., S.T., D.B., V.V.; writing—review & editing, M.d.C.S., L.G.-G., I.D., A.L., H.A., A.P.P., S.T., D.B., V.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research was co-funded by Foundation for Science and Technology (FCT) and FEDER funds through PORNorte under the project CoffeeRES ref. PTDC/ASP-PLA/29779/2017, and through PORLisboa, under the project PATHOmics ref. PTDC/ASP-PLA/29189/2017, and by FCT UNIT LEAF (UID/AGR/04129/2020).

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

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