Phytopathologia Mediterranea
The international journal of the
Mediterranean Phytopathological Union

Firenze University Press
www.fupress.com/pm

Review

Fomitiporia mediterranea M. Fisch., the historical Esca agent: a comprehensive review on the main grapevine wood rot agent in Europe

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Summary. *Fomitiporia mediterranea* M. Fisch. (*Fmed*) is a basidiomycete first described in 2002, and was considered up to then as part of *Fomitiporia punctata* (P. Karst) Murrill. This fungus can degrade lignocellulosic biomass, causing white rot and leaving bleached fibrous host residues. In Europe *Fmed* is considered the main grapevine wood rot (Esca) agent within the Esca disease complex, which includes some of the most economically important Grapevine Trunk Diseases (GTDs). This review summarises and evaluates published research on *Fmed*, on white rot elimination by curettage or management by treatments with specific products applied to diseased grapevines, and on the relationship between wood symptoms and Grapevine Leaf Stripe Disease (GLSD) in the Esca disease complex. Information is also reviewed on the fungus biology, mechanisms of pathogenicity, and their possible relationships with external foliar symptoms of the Esca disease complex. Information on *Fmed* control strategies is also reviewed.

Keywords. *Fmed*, Basidiomycete, white rot, wood symptoms, foliar symptoms.

OPEN ACCESS

Citation: Author (2021) Title. *Phytopathologia Mediterranea* 60(2): 351-379. doi: 10.36253/phyto-13021

Accepted: August 12, 2021

Published: September 13, 2021

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Competing Interests: The Author(s) declare(s) no conflict of interest.

Editor: Alan Phillips, University of Lisbon, Portugal.

INTRODUCTION

Grapevine Trunk Diseases (GTDs), mainly comprising Botryosphaeria dieback, Eutypiosis and the Esca disease complex, are widespread in vineyards (Mugnai *et al.,* 1999; Bertsch *et al*., 2013; Bruez *et al*., 2013; Mondello *et al*., 2018a). These diseases significantly affect grapevine productivity causing yield losses and quality degradation affecting wine alcohol content and flavour components (Mugnai *et al*., 1999; Lorrain *et al*., 2012; Calzarano *et al*., 2001, 2017).

For several decades the only effective pesticides used to control GTDs were sodium arsenite, to reduce the leaf stripe foliar symptoms in the Esca complex of diseases (Ravaz, 1919; Bonnet, 1926; Rui and Battel, 1963; Svampa and Tosatti, 1977; Del Rivero and García-Marí, 1984), and the fungicides benomyl and carbendazim, to reduce infections by the agents of Eutypiosis and Botryosphaeria dieback, respectively (Magarey and Carter 1986; Ramsdell, 1995). All these pesticides were banned in European countries in the early 2000s because of their potential environmental and/or user toxicities, more than 10 years after GTDs and especially Esca disease complex were becoming acute problems in Europe and in other grapevine growing countries. GTDs have been described as "the biotic stress of the century" for grapevines (Songy *et al*., 2019a), and all wine-growing countries are likely to be affected by these diseases. In France, the National Grapevine Trunk Disease Survey assessed incidence and evolution of GTDs during a 10 year survey period. Up to 13% of productive vines were affected by GTDs in French vineyards (Grosman, 2008; Grosman and Doublet, 2012; Bruez *et al*., 2013). In Italy, incidence of GTDs was between 8 to 19% (Romanazzi *et al*., 2009), and was of average annual incidence of 12% in vineyards younger than 10 years (Abbatecola *et al*., 2000), or up to 63% in 30 year old vineyards (Surico *et al*., 2000).

In several countries within and outside Europe, there has been an upward trend of GTDs since the end of the 20th century (Mugnai *et al*., 1999; Wicks and Davies, 1999; Rubio and Garzón, 2011; Úrbez-Torres *et al*., 2014; Fontaine *et al*., 2016a; Guérin-Dubrana *et al*., 2019; Kraus *et al*., 2019). GTDs have also caused severe economic losses. These have been estimated as up to $US 260 million in California (Siebert, 2001) for GTDs, and $US 2000 to 3000 per hectare for "Esca disease" (Vasquez 2007, in Rubio and Garzón, 2011), and approx. one billion euros in wine production due to GTDs in France (reported in 2014 by IFV, the French Wine Institute). Annual financial costs of dead vine replacements in all wine production countries were estimated to be 1.132 billion euros (Hofstetter *et al*., 2012). These losses have been the major reason that professional winegrowers, research agencies, financial consortia and the scientific community have concentrated on GTDs research in recent decades.

The complexity of symptoms and fungi involved in these diseases is great, and this is particularly true for "Esca disease" (in this paper, when the literature data refer to this generic term – as well as when we will arbitrarily refer to this generic term to avoid nomenclature confusion when critically discussing the literature – we will place quotation marks around the term "Esca disease"). Historically, Esca, a word of indo-european origin meaning "food", tinder for fire, used to indicate "amadou" i.e. white rot (Viala, 1922, on the chapter written by Gard in "Bulletin de la Societé de Pathologie Vegetale", 1922; Montanari, 2010), had been used for a grapevine wood rot disease. Later, the term was associated with foliar symptoms, described as chronic or acute forms (Viala, 1926; Larignon and Dubos, 1997; Letousey *et al*., 2010; Lecomte *et al*., 2012), and was shown to involve several different symptoms associated with different pathogens. It was then proposed as a disease complex involving multiple pathogens including basidiomycetes and/or ascomycetes (Mugnai *et al*., 1999; Surico, 2009; Bertsch *et al*., 2013). These caused separate diseases including: *i*) white rot (Esca) that develops mostly in old vines; *ii*) vascular diseases, widely present in propagation material and young vines (brown wood streaking of grape cuttings and Petri disease); and *iii*) Grapevine Leaf Stripe Disease (GLSD), which has an unusual epidemiology and symptomatology that can be associated with some or all of the wood pathogens, i.e. only vascular and canker agents, or, very often, also wood decay in all possible combinations. The condition where white rot (Esca) and GLSD occur together can be indicated as "Esca proper", in recognition of the original disease description.

The frequency of GLSD foliar symptoms has increased considerably over the last two decades. A preliminary study (Fussler *et al*., 2008) indicated mean incidence increase of 3.25% for "Esca disease" (leaf stripe and apoplexy symptoms) in France between 2003 and 2005. "Esca disease" and Eutypiosis were responsible together for 10% of vine replacements in Alsace (Kuntzmann *et al*., 2010). Also in France, Bruez *et al*. (2013) showed that incidence increase varied according to region. In Austria, Reisenzein *et al*. (2000) estimated a 2.7% annual increase of plants showing "Esca disease" foliar symptoms. In Italy, Surico *et al*. (2006) indicated an increase from 30 to 51% between 2000 and 2006, and Romanazzi *et al*. (2009) showed how disease incidences reached 60 to 80% in many old vineyards of south-

ern Italy. A comprehensive survey for 22 European and Mediterranean vine-growing countries (COST Action; Guérin-Dubrana *et al*., 2019) described GLSD trends in most surveyed countries as "increasing" and/or "worrying", particularly in France, Italy, Spain and Turkey. In Germany, in 12 intensively pruned vineyards of red and white grape varieties and resistant and traditional cultivars, incidence of GLSD increased from 1.9% in 2015 to 3.6% in 2018, and was greatest in 2017 at 4.5% of vines affected (Kraus *et al*., 2019).

Some observations on Esca complex of diseases are now well accepted, despite the complexity, terminology evolution, and difficulties in understanding the interactions of variables that affect symptom expression. These include:

i) The interactions with environmental, pedo-climatic and agronomic factors/practices that can affect symptom expression and disease severity (Marchi *et al*., 2006; Calzarano *et al*., 2018a; Lecomte *et al*., 2018; Fischer and Peighami-Ashnaei, 2019; Songy *et al*., 2019a).

ii) No completely resistant grape cultivar has been reported, but cultivar and clone contributions to symptom expression and severity have been observed and reviewed (Marchi, 2001; Quaglia *et al*., 2009; Murolo and Romanazzi, 2014; Kraus *et al*., 2019; Moret *et al*., 2019; Songy *et al*., 2019a; Moret *et al*., 2021).

iii) The nutritional (especially macronutrient) status of vines can affect foliar symptom expression (Calzarano *et al*., 2009, 2021).

iv) Although the presence of an exceptionally wide mycoflora in Esca- and GLSD-affected vines has been confirmed by meta-barcoding (Del Frari *et al*., 2019a; Niem *et al*., 2020), the pathogens most frequently associated with the wood infections are the two Ascomycota *Phaeomoniella chlamydospora* (W. Gams, Crous, M.J. Wingf. & L. Mugnai) (Crous and Gams, 2000) (*Pch*) and *Phaeoacremonium minimum* (Tul. & C. Tul.) Gramaje, L. Mostert & Crous (Gramaje *et al*., 2015) (*Pmin*) (syn. *Phaeoacremonium aleophilum*), while the most frequently isolated basidiomycete in Europe has been *Fomitiporia mediterranea* M. Fisch. (Fischer, 2002) (*Fmed*). The two Ascomycota species have mostly been associated with the "phaeotracheomycotic complex" (brown wood streaking, Petri disease and GLSD; Bertsch *et al*., 2013), while *Fmed* or the other basidiomycetes causing wood decay (Fischer and González-García, 2015) have only been associated with white rot, Esca and "Esca proper". Nevertheless, decay elimination (curettage) reduced foliar symptoms, and correlations between white rot extent, elimination and foliar symptom expression have been reported (Maher *et al*., 2012; Thibault, 2015; Cholet *et al*., 2019, 2021; Pacetti *et al*., 2021).

Fomitiporia mediterranea (as *Fomitiporia punctata*) was shown to be a primary pathogen by artificial inoculations, either in vineyards or in greenhouse experiments (Sparapano *et al*., 2000a; 2001a). The need for specific successions of fungi in wood colonization to detoxify wood cellular microenvironments from excesses of polyphenols produced by plant reactions has been suggested but was never fully proved (Larignon and Dubos, 1997; Mugnai *et al*., 1997; Amalfitano *et al*., 2000). Microbial combinations between *Fmed*, *Pch* and some bacterial taxa (i.e. *Sphingomonas* spp. and *Mycobacterium* spp.) may have a role in the onset of "Esca disease" in young vines (Bruez *et al*., 2020). Synergism between *Fmed* and bacteria such as *Paenibacillus* spp. for grapevine wood component degradation has also been confirmed (Haidar *et al*., 2021).

Despite the year-to-year fluctuations in incidence, foliar symptom surveys represent simple and non-invasive ways to indirectly assess grapevine wood infection by Esca complex pathogens, and for determining epidemiology, crop losses and health status of vineyards (Guérin-Dubrana *et al*., 2013). Claverie *et al*. (2020) summarised knowledge on foliar symptom outbreak in the "toxins hypothesis" and "hydraulic dysfunction hypothesis". The first describes how phytotoxic compounds produced by "Esca disease"-associated fungi could diffuse through host transpiration stream sap flow to leaves, inducing the typical tiger-striped leaf patterns (Abou-Mansour *et al*., 2004; Bruno and Sparapano, 2006b; Andolfi *et al*., 2011). The second hypothesis explains how impairment of sap flow to leaves, mainly caused by vessel occlusions/pathogen compartmentalization, could lead to cavitation contributing to foliar symptom expression (Pouzoulet *et al*., 2014, 2017, 2019). Recent findings, however, suggest how these two hypotheses can be complementary and not exclusive, due to observed association between foliar symptoms, disruption of vessel integrity and presence of some "Esca disease"-associated pathogens presence in host trunks, which could elicit a distance-response (Bortolami *et al*., 2019). Stem vessel occlusion has been related to exacerbation of foliar symptom expression in the following growth season (Bortolami *et al*., 2021).

Because the two Ascomycota *Pch* and *Pmin* have frequently been associated with foliar symptoms of "Esca disease"-symptomatic plants, considerable research has been carried out on *Pch* and *Pmin* biology and pathogenicity, and a more comprehensive and integrated view on these species was presented by authors such as Valtaud *et al*. (2009), Mostert *et al*. (2006) and Gramaje *et al*. (2015). The same cannot be affirmed for *Fmed*. Despite progress made since taxonomic description of this fungus (Fischer, 2002), knowledge on the pathogen, its wood

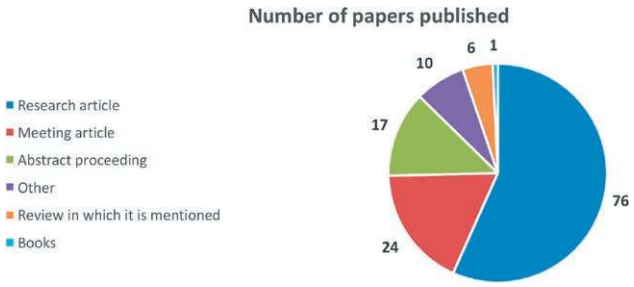

Figure 1. Number of published papers dealing with *Fomitiporia mediterranea* from 2002 (*Fmed* identification date) to 2021, as indexed in the Web of Science™ database (Thomson Reuters).

degradation process and relationship with the other Esca complex diseases, is fragmented. There are few reviews which consider *Fmed* as part of "Esca disease" or GTDs in general, and to our knowledge no comprehensive review on *Fmed* alone has been undertaken (Figure 1).

For this reason, along with contrasting reports of correlations between amounts of white rot necrotic tissues (thus *Fmed* presence) and the leaf stripe symptoms (Maher *et al*., 2012; Bruez *et al*., 2014; Bruez *et al*., 2020; Cholet *et al*., 2021; Pacetti *et al*., 2021), and reports of little or no correlation between these factors (Edwards *et al*., 2001; Calzarano and Di Marco 2007; Romanazzi *et al*., 2009; Mugnai *et al*., 2010), a review of *Fmed* is necessary, in order to collect knowledge of the fungus itself, and to stimulate scientific debate and novel ideas in the context of GTDs.

BASIDIOMYCETES ASSOCIATED WITH ESCA

Knowledge on basidiomycetes associated with "Esca disease" has increased, and Fischer (2006), Fischer and González-García (2015), and Cloete *et al*. (2015a, 2016) provided a comprehensive compendium on the topic. Ravaz (1909) was a pioneer in grapevine basidiomycete identification, with the putative identification of *Phellinus igniarius* (L.) Quél. (at the time *Fomes igniarius* (L.) Fr. and formerly *Polyporus igniarius* (L.) Fr. based on fruit bodies found on diseased grapevines in southern France). Vinet (1909) and Viala (1926) also reported the presence of *Stereum hirsutum* (Willd.) Pers. in French vineyards. These two basidiomycetes were long considered as causal agents of Esca wood decay but pathogenicity was only proven for *P. igniarius* (most likely a *Fomitiporia* sp.) by Chiarappa (1997).

Studies on "Esca disease" and its etiology multiplied in the late 1990s, especially when Larignon and Dubos (1997) isolated *Phellinus punctatus* (P. Karst.) Pilát from Esca wood decay in French vineyards. After studies of the infrageneric structure of *Phellinus* s.l. by Fiasson and Niemelä (1984), Fischer (1996) and Wagner and Fischer (2001, 2002), *P. punctatus* was grouped within *Fomitiporia*, as *F. punctata* (P. Karst) Murrill (= *P. punctatus*). Multiple surveys of Italian vineyards by Cortesi *et al*. (2000) concluded that the main cause of decay in Esca-affected vines was *F. punctata*, later recognized as the new species *F. mediterranea* (Fischer 2002), which is now considered the main white rot agent in "Esca disease" in Europe and Mediterranean regions.

Stereum hirsutum was isolated by Larignon and Dubos (1997) from central decayed grapevine wood inhabited by putative *P. igniarius*, but its role in GLSD is still debated, although it is clearly a white rot basidiomycete agent. Some authors have suggested that this fungus has little or no role in the Esca complex of disease because it is found only rarely in vineyards (Mugnai *et al*., 1999; Cortesi *et al*., 2000; Reisenzein *et al*., 2000; Vicent *et al*., 2001). In any case, *S. hirsutum* may act as a weak facultative parasite, occasionally penetrating the heartwood of host plants and producing very limited infections and decay of the inner host tissues (Fischer and González-García, 2015).

Many other basidiomycetes have been isolated from decaying grapevine wood. White *et al*. (2011) characterised ten possibly novel taxa belonging to *Hymenochaetales* associated with "Esca disease", *i.e.* white rot on GLSD symptomatic vines. For Europe, an annotated checklist of GTD-related basidiomycete taxa has been published (Fischer and González-García, 2015). With the advent of metagenomic approaches, reports of basidiomycetes are increasing (Del Frari *et al*., 2019a; Bruez *et al*., 2020). A recent study by Brown *et al*. (2020) aimed to clarify the relevance of basidiomycete colonisation within the Esca complex of diseases. They isolated many taxa (including new species, such as *Inonotus vitis* A.A. Brown, D.P. Lawr. & K. Baumgartner, *Tropicoporus texanus* A.A. Brown, D.P. Lawr. & K. Baumgartner, and *Fomitiporia ignea* A.A. Brown, D.P. Lawr. & K. Baumgartner) from white rot and black/brown discoloured wood collected from grapevine plants expressing GLSD foliar or shoot symptoms in Californian and Texan vineyards.

More *Fomitiporia* spp. have been associated with "Esca-diseased" grapevines in other regions, including *Fomitiporia australiensis* M. Fisch., Jacq. Edwards, Cunningt. and Pascoe in Australia (Fischer *et al*., 2005), *Fomitiporia polymorpha* M. Fisch. in California (Fischer and Binder, 2004), *Fomitiporia capensis* M. Fisch., M. Cloete, L. Mostert, F. Halleen in South Africa (Cloete *et al*., 2014), *F. ignea* (Brown *et al*., 2020) in Texas, and, more recently, *Fomitiporia punicata* Y.C. Dai, B.K. Cui & Decock in China (Ye *et al*., 2021), originally described

on *Punica granatum* (Dai *et al*., 2008). As well, *Fomitiporia erecta* A. David, Dequatre & Fiasson, and *F. punctata* were mentioned as occurring on grapevine in Spain (Fischer and González-García, 2015). Of these species, *F. australiensis*, *F. capensis* and *F. ignea* were exclusively documented from grapevine.

Geographic distribution and host range of *Fmed* have probably expanded in recent decades. This is supported by the number of host plants in the different regions. In Central Europe the host range is largely limited to *Vitis vinifera*, given the scarcity of reports of the fungus on other hosts: i.e. on *Laurus nobilis* (Fischer, 2006) and on *Robinia pseudoacacia* (Schmidt et. al., 2012). However, *Fmed* occurs on several other hosts in the Mediterranean area (see below). This discrepancy in the reported host range indicates a recent invasion of the fungus into the viticultural regions of Central Europe, possibly associated with climatic changes leading to increased temperatures in this region.

These observations indicate that intrinsic geographic and climate conditions play roles in diffusion of Basidiomycota pathogens and influence spread of *Fomitiporia* spp. in vineyards (Fischer *et al*., 2005; Fischer, 2006; Cloete *et al*., 2014). Geographical variations influence distribution of fungi among different locations (Hofman and Arnold, 2008; Dietzel *et al*., 2019), and climate is a major abiotic factor shaping fungal biogeography (Castillo and Plata, 2016; Větrovský *et al*., 2019). Spatial analyses of "Esca-disease"-related basidiomycete taxa, and comprehensive screening of possible non-*Vitis* host plants, preferably from proximity of vineyards, could help to identify key pedo-agroclimatic factors affecting their diffusion, and could indicate why some *Fomitiporia* spp. are retrieved from some areas but not others.

In Europe information on grapevine white rot agents began to be revised in 2002: Fischer found that strains formerly acknowledged as *F. punctata* collected from grapevines in Italy and Germany differed from strains from other hosts and other geographic areas (Central Europe). Molecular diagnoses (ITS data), pairing tests of single spore isolates, compared with temperature preferences of cultured mycelia allowed description of the new species *Fomitiporia mediterranea* M. Fischer (Fischer, 2002). This is currently considered the main causal agent of white rot in "Esca diseased" grapevines in Europe and in Mediterranean climate areas, while *F. punctata* is more ubiquitous, although a European centred distribution has been suggested by Decock *et al.* (2007).

Due to indistinguishable morphology between *Fmed* and *F. punctata*, but the highlighted phylogenetic differences, previous isolates and findings attributed to *F. punctata* should be reconsidered as possibly assignable to *Fmed* (Fischer, 2002; Ciccarone *et al*., 2004; Fischer, 2006). Recent findings on *P. punctatus* and *P. pseudopunctatus* A. David Dequatre and Fiasson by Polemis *et al.* (2019) and Markakis *et al.* (2019) have reinforced that possible misidentification led to the underestimation of *F. mediterranea* incidence in the Mediterranean region.

This review focuses only on *Fmed* and its role in Esca-related wood degradation, with careful reconsideration of previous reports where the pathogen may have been incorrectly identified.

IDENTIFICATION, TAXONOMY, HOST RANGE, AND SYMPTOMS INDUCED IN GRAPEVINES

Description of fruit bodies and mycelia

Morphology and anatomy of *Fomitiporia mediterranea* (*Hymenochaetaceae*, *Hymenochaetales*, *Agaricomycetes*, *Basidiomycota*) were described by Fischer (2002).

Fomitiporia mediterranea fruiting bodies (Figure 2) are resupinate, inseparable, and hard woody, up to 15 mm thick with yellowish-brown narrow margins, containing subglobose to oval basidiospores. The hyphal system is dimitic, with generative and skeletal hyphae. Detailed descriptions of the hyphal system, fruiting bodies and basidiospores of this fungus were provided by Fischer (2002, 2009) and Fischer and González-García (2015).

Figure 3, A, B and C show, respectively, a tube mouth with outgrowth of vegetative hyphae, outgrowing hyphae from naturally infected grapevine wood and the pore surface of a fruiting body of *F. mediterranea*.

After isolation from infected wood and/or fruit bodies, mycelial isolates may develop into a so-called "bleaching type" (Type B: Fischer, 1987) or a "staining type" (Type S: Fischer, 1987) (Figure 4).

Type B mycelium has a cottony to woolly appearance, and aerial hyphae are yellowish to brown. Medium pigmentation is sparse or absent. Type S-mycelium has sparse aerial hyphae, and medium pigmentation is strong. Colony growth after 14 days at 21°C on Malt Extract (ME) agar in complete darkness was more rapid in bleaching-type isolates (colony diameter = 3.0 to 4.5 cm) than staining-type isolates (1.5 to 2.5 cm). The two mycelium types may alternate over ensuing inoculations. Growth was confirmed between 15 and 35°C, with optimum growth at 30°C (Fischer, 2002, 2006; Fischer and Kassemeyer, 2003). Under laboratory conditions, sporulation is absent in *Fmed*. Spore germination tests with spores from actively sporulating fruit bodies were performed for some *Fmed* strains, indicating very low germination rates (less than 1%) with a high variation in germination times (Fischer, 2002).

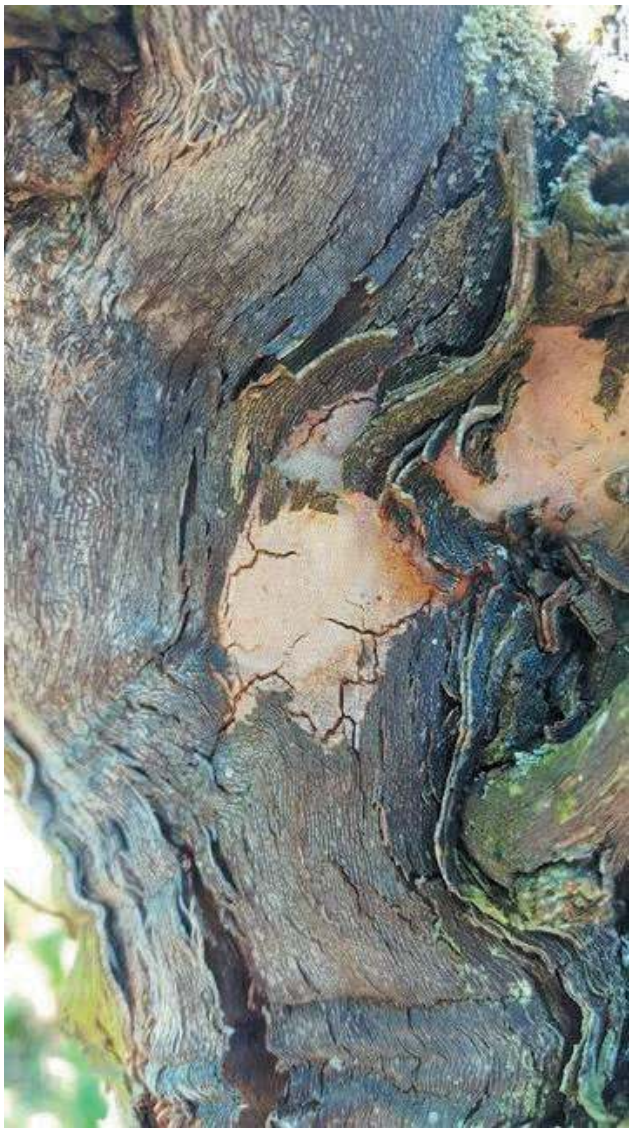

Figure 2. Fruiting bodies of *Fomitiporia mediterranea* on a grapevine trunk. Photograph taken in July 2018, from 'Sauvignon Blanc', in a vineyard in Ehrenkirchen, Germany.

Spread by basidiospores is considered the main dispersal form for *Fmed* and this has been described to be mainly via rain and wind (Cortesi *et al*., 2000). In Central European vineyards, fruiting body sporulation is increased after rainy periods and is related to daily temperatures greater than 10°C and relative humidity greater than 80% (Fischer, 2009).

Mating system

Studies of the *Fmed* mating system were also affected by misidentification of the pathogen. Fischer

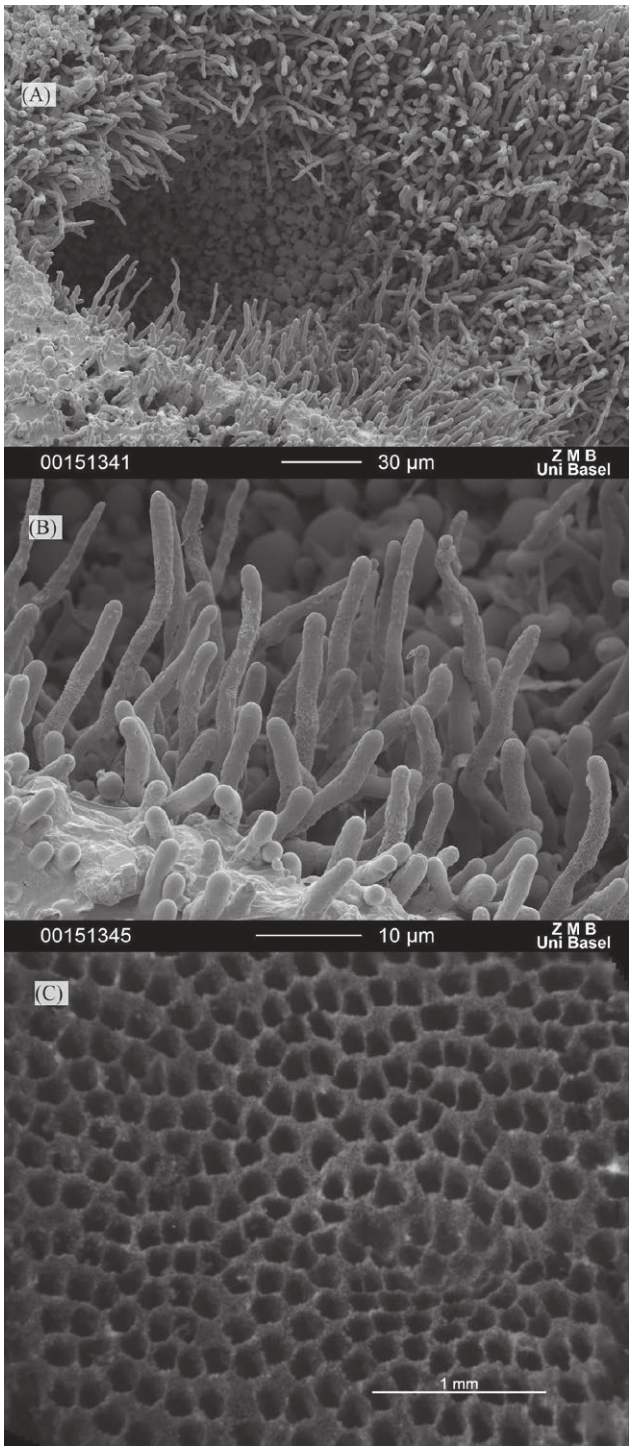

Figure 3. (**A**), Cryo-Scanning-Electron-Microscopy (Cryo-SEM) micrograph (×500 magnification) of an *Fmed* tube mouth showing outgrowth of vegetative hyphae. (**B**), Cryo-SEM micrograph (×2,000) of hyphae in a cross section of a grapevine trunk naturally affected by white rot. (**C**), Stereo micrograph of the surface of an *Fmed* fruiting body (×50) The pores are 5-8/mm. The diseased grapevine specimen was collected in a vineyard in Pfaffenweiler, south-west Germany.

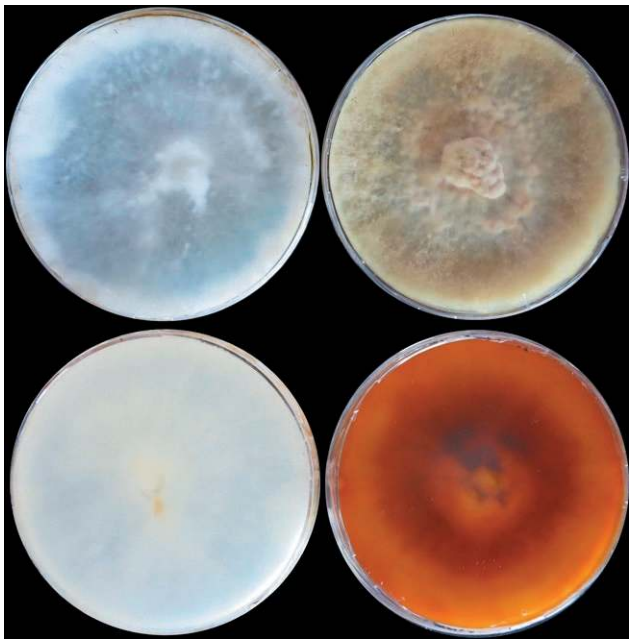

Figure 4. Mycelium cultures of *Fomitiporia mediterranea* on malt extract agar (ME) after 28 days of incubation. "Type B" (left, surface and reverse side) and "Type S" (right, surface and reverse side).

(1996) described *F. punctata* strains (later distinguished from *Fmed*) as homothallic, with no mating types evident in pairings of spores originating from one fruiting body. The time lag between separation of *Fmed* from *F. punctata* by Fischer (2002) and the research of Jamaux-Despreaux and Péros (2003) initially provided conflicting reports of the homothallic mating system described for the fungus. Jamaux-Despreaux and Péros (2003) observed outcrossing populations in France and Italy. This was indicated by high genetic variation within and between vineyards, and random assortment of genetic markers. They therefore suggested possible existence of non-outcrossing populations in other areas. Following correct assignment of species, it was shown that *Fmed* was a heterothallic bipolar species (Fischer, 2002), while *F. punctata* was confirmed as homothallic.

A variety of pairing tests were conducted by Fischer (2002), who demonstrated a range of compatible and incompatible reactions (see Fischer, 2002 for details). Growth of secondary mycelia was stronger in compatible inter-strain than in intra-strain pairings. Mycelia formed from inter-strain pairings could prevail under natural conditions, resulting in high outcrossing rates.

It is now accepted that basidiomycete mating is regulated by different genes, grouped in two types of homeodomain transcription factors (*HD genes*), in pheromones genes and their related receptors and response genes (*PR genes*). These genes can reside in linked or un-linked chromosome loci (James *et al*., 2006; Kües *et al*., 2013, 2015). James *et al*. (2013) highlighted at least four *HD* (two pairs of *HD1* and two pairs of *HD2*), and several apparently functional *PR genes* in the *Fmed* genome, such as 2 *STE3*, several *MAP* kinases and 3 *Prf1*. These authors also suggested that the genes were not linked in a unique mating locus (James *et al*., 2013; Kües *et al*., 2015).

Further pairing tests, perhaps with other strains, could better clarify the dispersal system of the fungus, and identify other possible intersterility groups. This would be further clarified if genetic variability data retrieved from German vineyards were considered. Fischer (2012) found 14 different *Fmed* genotypes out of 15 fruit bodies, all derived from one vineyard. Lentes and Fischer (personal communication) identified 56 genotypes out of 64 isolated mycelia, derived from different vines in two vineyards in the Moselle region of Germany.

Available *Fmed* genome could provide new information for expression analysis of mating-associated genes, especially in response to changing environmental conditions which are increasingly affecting European vineyards. Increasing this knowledge could provide a better understanding on pathogen spread and genetic recombination, since *Fomitiporia* spp. are well adapted to different conditions and climates, as reflected by their biogeographical variability.

Field identification

Compared to white rot presence, fruiting bodies of *Fmed* are very rarely found in vineyards, mostly on the uppermost parts of trunks, near pruning wounds, which are the main sites of infection (Cortesi *et al*., 2000; Fischer *et al*., 2005; Fischer, 2006; Fischer and González-García, 2015). In vineyards in Central Europe, *Fmed* fruiting bodies were only present on 1 to 3% of "Esca-diseased" grapevines that were older than 15 years (Fischer, 2009), and the pathogen was detected as vegetative mycelium in infected hosts. In Germany, a 100:1 ratio is mentioned by Fischer (2006) indicating a low co-occurrence of vegetative mycelium with white rot and fruiting bodies. This was also reported in Tuscan vineyards by Cortesi *et al*. (2000). Because compatibility groups were identified (Fischer, 2002), the occasional occurrence of fruiting bodies in vineyards may be partly explained by the possibly rare contact between sexually compatible basidiospores (Jamaux-Despreaux and Péros, 2003). Dead grapevine trunks are the most favourable substrates for development of fruiting bodies, and the dead trunks are usually removed from vineyards. Another hypothesis to explain the low ratio between white rot and fruiting bodies in non-Central European countries is that the disease

Table 1. Host range and geographic distribution of *Fomitiporia mediterranea* M. Fischer 2002. For each host (and each country), the table includes first reports which used classical isolations, and some of the significant subsequent reports/studies which used molecular classification and metagenomic approaches. References accompanied by "†" refer to studies which used former classifications (as *Phellinus punctatus* or *F. punctata*) which should be carefully reconsidered as representing *F. mediterranea*.

Host	Country	References
Vitis vinifera	Algeria	Berraf and Péros, 2005
	Austria	Fischer *et al*., 2006
	Czech Republic	Baranek *et al*., 2018
	France	†Larignon and Dubos, 1997; †Jamaux-Despreaux and Péros, 2003; Péros *et al*., 2008; Laveau *et al*., 2009; Kuntzmann *et al*., 2010; Ouadi *et al*., 2019; Bruez *et al*., 2020
	Germany	Fischer, 2002; Fischer and Kassemeyer, 2003; Fischer, 2006; Fischer, 2012; Fischer and González-García, 2015; Fischer, 2019
	Greece	†Rumbos and Rumbou, 2001
	Hungary	Rábai *et al*., 2008
	Iran	†Karimi *et al*., 2001; Farashiyani *et al*., 2012; Mohammadi *et al*., 2013; Rajaiyan *et al*. 2013; Amarloo *et al*.,2020; Mirabolfathy *et al*., 2021
	Italy	†Mugnai *et al*., 1999; †Cortesi *et al*., 2000; Ciccarone *et al*., 2004; Romanazzi *et al*., 2009; Quaglia *et al*., 2009; Del Frari *et al*., 2019a; Girometta *et al*., 2020; Pacetti *et al*., 2021
	Lebanon	Choueiri *et al*., 2014
	Portugal	Sofia *et al*., 2006
	Slovenia	Rusjan *et al*., 2017
	Spain	†Armengol *et al*., 2001; Martin and Cobos, 2007; Sánchez-Torres *et al*., 2008; Luque *et al*., 2009; Garcia Benavides *et al*., 2013; Elena *et al*., 2018
	Switzerland	Fischer, 2006
	Turkey	Akgül *et al*., 2015
Acer negundo	Italy	Fischer, 2002
Actinidia spp.	Greece	†Elena and Paplomatas, 2002
	Italy	Fischer, 2002; Di Marco *et al*., 2004a; Di Marco and Osti, 2008; Girometta *et al*., 2020
Albizia julibrissin	Greece	Markakis *et al*., 2017
Cistus sp.	Italy	Girometta *et al*., 2020
Citrus spp.	Greece	Elena *et al*., 2006
	Italy	Roccotelli *et al*., 2014
Corylus avellana	Italy	Pilotti *et al*., 2010; Girometta *et al*., 2020
Elaeagnus angustifolia	Iran	Ahmadyusefi and Mohammadi, 2019
Fagus sylvatica	Italy	Girometta *et al*., 2020
Fortunella japonica	Greece	Markakis *et al*., 2017
Hedera helix	Italy	Girometta *et al*., 2020
Lagerstroemia indica	Italy	Fischer, 2002
Laurus nobilis	Slovenia	Fischer, 2006
Ligustrum vulgare	Italy	Fischer, 2006
Olea europaea	Greece	†Paplomatas *et al*., 2006; Markakis *et al*., 2017; Markakis *et al*., 2019
	Italy	Fischer, 2002 ; Carlucci *et al*., 2013
Platanus x acerifolia	Italy	Pilotti *et al*., 2005
Prunus dulcis	Spain	Olmo *et al*., 2017
Punica granatum	Greece	Markakis *et al*., 2017
Pyrus communis	Greece	Markakis *et al*., 2017
Quercus ilex	Italy	Fischer, 2006
Quercus robur	Italy	Girometta *et al*., 2020
Quercus rubra	Italy	Girometta *et al*., 2020
Robinia pseudoacacia	Italy	Fischer, 2006; Girometta *et al*., 2020
	Germany	Schmidt *et al*., 2012
Salix alba	Italy	Girometta *et al*., 2020
Ulmus spp.	Iran	Mirsoleymani and Mostowfizadeh Ghalamfarsa, 2019

and fungus structures could occur in several alternative hosts within or near vineyards (see Table 1). These sources of inoculum could be important. The discrepancies between occurrence of vegetative mycelia and fruit bodies are often large in lignicolous fungi. While the existence of *F. mediterranea* fruiting bodies may be underestimated (Fischer 2006), precise evaluation of exogenous inoculum sources remains a challenging issue.

Field identification of *Fomitiporia* spp. on grapevines is often complex. Because fruiting bodies are very rare and have very similar morphologies, molecular diagnoses after isolations from infected wood tissues or fruiting bodies are likely to be the most reliable tools for identification of mycelia not clearly assignable to particular species (Ciccarone *et al*., 2004).

Overview of molecular diagnosis, taxonomy and phylogeny

Amplifications and sequencing of ITS regions with or without Large Sub-Unit (LSU) translation elongation factor subunit 1-α (*tef1*) and the second largest subunit of RNA polymerase II (*RPB2*) sequence analysis, have permitted new advances in classification of grapevine basidiomycetes using specific primers. Reports are increasing, differentiating new *Fomitiporia* species (Cloete *et al*., 2016; Chen and Cui, 2017; Brown *et al*., 2020; Chen *et al*., 2021; Ye *et al*., 2021).

Fischer (2002) reported a specific method for identification, based on the nuclear encoded ribosomal DNA region ITS1-5.8S-ITS2 using the primer pair prITS5 and prITS4 (White *et al*., 1990). Compared to other *Fomitiporia* spp., *Fmed* strains showed unique small insertions in both ITS regions: between nucleotides 201 and 206 (AATAAT) in ITS1 and between nucleotides 748 and 745 (CCTTTGA) in ITS2 (Fischer, 2002; 2006; Fischer and Binder, 2004). Since 2006, specific primers based on these insertions have been available for differentiation of *Fmed* from other species such as *F. punctata* and *F. australiensis* (Fischer, 2006). The primer sequences and characteristics are as follows: pr*Fmed*1, 5′ GCA GTA GTA ATA ATA ACA ATC 3′ (GC = 28.6%, TM = 50.1°C); and pr*Fmed*2, 5′ GGT CAA AGG AGT CAA ATG GT 3′ (GC = 45%, TM= 55.3°C). A 550 bp product is only obtained for *Fmed*. Parameters for successful amplification were described by Fischer (2006).

With basidiospores being the main dissemination agent of *Fmed*, considerable genetic variation in *F. punctata* (probably *Fmed*) has been described by Random Amplified Polymorphic DNA (RAPD) markers. This variation has been shown among isolates derived from individual vineyards (Pollastro *et al*., 2000; Jamaux-Despreaux and Péros, 2003). Pollastro *et al*. (2001) successfully developed sequence-characterised amplified region (SCAR) primers suitable as a molecular diagnostic tool for *Fmed*.

The primer pair ITS1 and ITS4 (White *et al*., 1990) have also been successfully used for identification of *Fmed* isolates within an Italian mycological collection based on fresh mycelial isolates (Girometta *et al*., 2020).

Other *Fomitiporia* species recorded from grapevine include: *F. polymorpha*, *F. capensis*, *F. australiensis*, *F. ignea*, *F. erecta*, *F. punctata*, and *F. punicata*. For *F. polymorpha, F. australiensis*, *F. erecta* and *F. punctata*, characterization of the ITS1-5.8S-ITS2 region was sufficient either to describe them as separate species, or to establish phylogenetic relationships with other *Fomitiporia* spp. (Fischer and Binder, 2004; Fischer *et al*., 2005; Fischer and González-Garcia, 2015). Implication of other conserved genetic regions has distinguished these other species above metioned, using the LSU unit ribosomal RNA-enconding regions *tef1* and *RPB2* together with ITS data to describe them (Cloete *et al*., 2014; Brown *et al*., 2020; Ye *et al*., 2021). Nevertheless, species-specific primers are available only for *Fmed* (Fischer, 2006), although unique forward primers paired with ITS4 primers have been designed to successfully detect *F. capensis* (Bester *et al*., 2015).

Host range and geographical distribution

Fomitiporia mediterranea is considered to be a highly adaptable species, based on the diversity of host plants, and occurrence in different regions and climates.

Isolates from grapevine were retrieved from a range of climate conditions, according to the most updated version of the original Köppen-Geiger climate classification map (Geiger, 1961; Beck *et al*., 2018): from "Mediterranean and temperate humid-subtropical climates" (for most of non-Central European isolates of the pathogen), to "arid and semi-arid climate" (for Algerian, Iranian and some of the non-Central European isolates), to "cool temperate climate" (for most of the Central-European isolates)" (see Figure 5 for the detailed geographical distribution of *Fmed*). Throughout its geographical range, *Fmed* shows close affinity with *V. vinifera*. However, this may be due to the economic significance of grapevine in these regions, resulting in detailed field observations for vineyards compared with other woody hosts. The fungus is also found on other host plants outside non-Central European countries, potentially resulting in increased infection pressure on grapevines (see Table 1 for a detailed list of hosts in different countries). Fischer (2002, 2006) postulated that, at least for non-Central European countries, alternative hosts could be foci for development of *Fmed* fruiting bodies, reinforcing the observed high adaptability of the pathogen to mul-

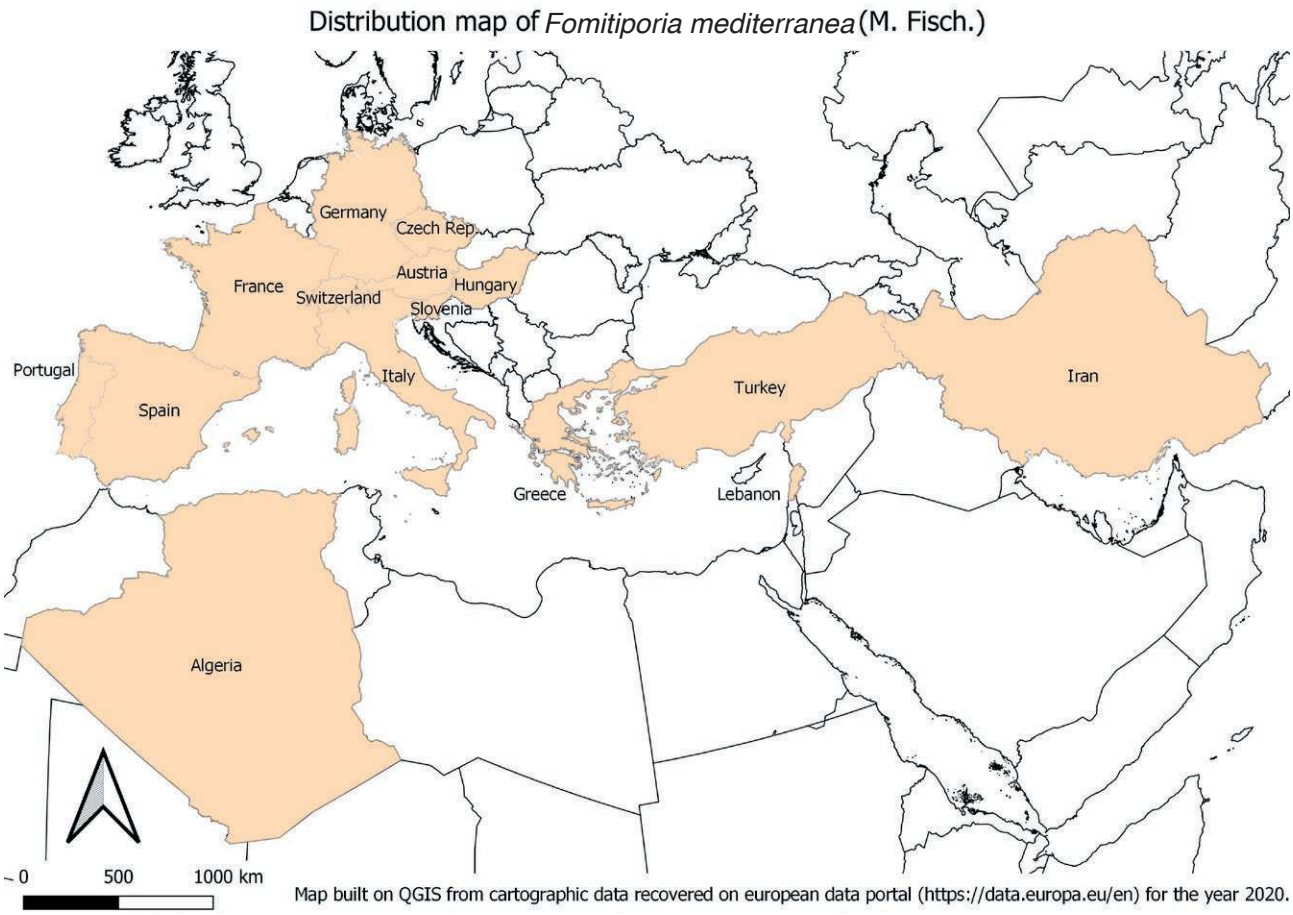

Figure 5. Distribution of *Fomitiporia mediterranea*, based on published reports of isolation of the fungus from grapevine, *Vitis vinifera*. The map was constructed using QGIS software (version 3.10.9-A Coruña).

tiple host species. Although current data show only very few isolations of *Fmed* from Central-European non-*Vitis* hosts, i.e. *Robinia pseudoacacia* in Germany (Schmidt *et al*., 2012) and *Laurus nobilis* in Slovenia (Fischer, 2006), the potential for the fungus to colonize other hosts is demonstrated. Future studies could focus on: *i*) surveys of fruiting body incidence on alternative hosts in the proximity of vineyards (to better assess inoculum sources); *ii*) performing comparative secretome and metabolome assessment of wood from different hosts to increase knowledge on *Fmed* colonization and growth and fruiting body development; and *iii*) determine pathogenicity to grapevine of isolates from different host plants.

Spread in grapevines and vineyards, wood symptoms and their relationships with foliar symptoms

Fomitiporia mediterranea is mainly retrieved from grapevine white rot necrotic tissue, although its presence in necrosis borders between white rot and non-necrotic tissues, and adjacent non-necrotic but recently colonised wood has been demonstrated (Fischer, 2002; Péros *et al*., 2008; Surico, 2009; Bruez *et al*., 2017; Elena *et al*., 2018; Bruez *et al*., 2021; Pacetti *et al*., 2021). The pathogen needs some time to colonise and decay woody tissues, explaining why it is predominantly found in trunks greater than 10 years old, and only to a lesser extent in young trunks (Sánchez-Torres et al., 2008; Fischer, 2009). White rot has also been mostly reported in old vineyards although it can be sometimes found in young vines and very occasionally in young GLSD symptomatic vines (Edwards *et al*., 2001; Mugnai *et al*., 2010).

In the Esca complex of diseases, several diseases have been recognised and have been related to infections by different fungi, and symptom expression can be influenced by many agronomic and environmental factors (cultural practices, host plant age, soil type, weather conditions) (Calzarano *et al*., 2018a; Gramaje *et*

al., 2018; Lecomte *et al*., 2018). Distribution of symptomatic vines within a vineyard poorly indicates the dissemination mode of related fungi, including *Fmed*, but diseased vines can be found grouped along vineyard rows. This supports the hypothesis that human-mediated practices are involved in pathogen spread (Mugnai *et al*., 1999; Guérin-Dubrana *et al*., 2019). Research on *F. punctata* (likely *Fmed*) isolates obtained from different vines showed they belonged to different somatic incompatibility types (Cortesi *et al*., 2000), indicating that each vine was colonised by genetically distinct individuals. Similarly, results for *F. punctata* (likely *Fmed*) (Jamaux-Despreaux and Péros, 2003) on the genotypic differences at vineyard level strongly indicated outcrossing reproduction via basidiospores. These results are not consistent with the hypothesis that *Fmed* is spread through wounds by pruning tools. In addition to this genetic evidence, much epidemiological data has shown that "Esca disease" symptoms were spatially random in vineyards (Cortesi *et al*., 2000; Surico *et al*., 2000; Sofia *et al*., 2006, Li *et al*., 2017), which is consistent with the hypothesis that basidiospores are the likely agents of dispersal for *Fmed* (Cortesi *et al*., 2000; Fischer, 2002). Although sporulation is rare on grapevine trunks, the inoculum could come from the many other hosts of the pathogen.

Typically, *Fmed* induces white rot in innermost grapevine wood (Figure 6). The decay is most often observed in arms, stem heads and trunks, with colonisation starting from pruning wounds and extending along entire trunks, mostly in the central parts but occasionally also at trunk bases, with desuckering wounds as entrance points (Larignon and Dubos 1997; Mugnai *et al*., 1999, 2010; Sparapano *et al*., 2000a, 2001a; Fischer, 2002; Fischer and Kassemeyer, 2003).

Rot diameters vary and decrease from infection origin points to boundaries with healthy wood (Mugnai *et al*., 2010). Rootstocks are rarely affected because vines die before white rot reaches rootstock tissues, although white rot has been reported in rootstock tissues (Maher *et al*., 2012; Elena *et al*., 2018). However, *Fmed*-related white rot is common in rootstock mother plants (Fischer, 2019).

The main symptom induced by *Fmed* on grapevines is spongy yellowish or bleached decay in wood tissues, but the relationship between wood and external foliar symptoms of "Esca diseased" grapevines is debated. To the best of our knowledge, Lafon (in 1921) was the first author to make this association. He assumed that *P. ignarius* (most likely a *Fomitiporia* sp.) present in the decay was the main agent responsible for the apoplectic form of "Esca disease" and leaf dessication (due to sap flow impairment). However, information on *Fmed*,

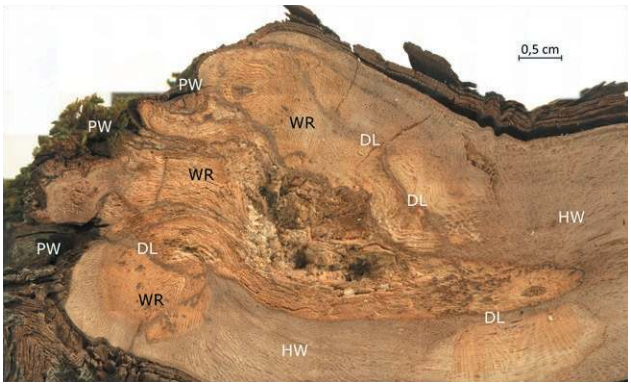

Figure 6. Macroscopic observation by stereo microscopy (×12 magnification) of a cross section (1 cm thick) of the head of a grapevine stem with a large area of white rot (WR) spreading from pruning wounds (PW) into healthy wood (HW). The necrotic zones are separated from the healthy wood by demarcation lines (DL). Specimen collected in May 2021 from a 28-year-old 'Sauvignon Blanc' plant, from a vineyard in Pfaffenweiler, south-west Germany.

grapevine wood symptoms and foliar symptoms needs to be re-examined. Demonstration of *Fmed* to act as a primary grapevine pathogen – after artificial inoculations by mycelial plugs or toothpicks (Sparapano *et al*., 2000a, 2001a) – confirms the importance of this pathogen within the Esca disease complex. However, research on the actual colonization sequence of "Esca disease"-associated fungi in field-grown grapevines is still required to increase knowledge of relationships between wood decay and foliar symptoms. Under field conditions, basidiospores can be infection agents, and artificial basidiospore inoculations in greenhouses would help to determine the colonization ability of *Fmed* and its role in foliar symptoms. However, basidiospores are difficult to obtain, and rarely germinate under laboratory conditions (Fischer, 2002). Therefore reviewing studies from last two decades will provide insights on the impacts of *Fmed* on "Esca disease" foliar symptoms (GLSD).

Different types of necrosis have been described in "Esca diseased" wood (Larignon and Dubos, 1997). White rot necrosis clearly shows the presence of *Fmed*, which has been the main isolation source of this pathogen in Europe (Larignon and Dubos, 1997; Mugnai *et al*., 1999; Bruez *et al*., 2017). Through logistic regression analyses in an old 'Cabernet Sauvignon' vineyard, Maher *et al*. (2012) analysed data from presumably 20 to 25 year-old vineyards, and assumed white rot to be the tissue type most strictly associated with the leaf stripe symptoms. A relationship between *Fmed* and "Esca disease" foliar symptoms (GLSD) was shown if white rot presence overcame a 10% necrosis threshold, in vine grafts and/or cordons. Using a similar approach, Calzarano and Di Marco (2007)

showed that, in 32- and 36-year-old vineyards, there was no relationship between severities of wood deterioration and external foliar symptoms. The leaf-symptomatic vines percentage with discoloration (but no white rot) was 46.2% in 32-year-old vineyards and 7.2% in 36-year-old vineyards. Both of these findings have been supported by other authors. Bruez *et al*. (2014) found white rot tissue in cordons from 79% of GLSD-symptomatic 10-year-old vines. Fischer (2012) found 100% of 366 trunks of 28-year-old 'Traminer' vines to be affected by white rot, but less than 10% had foliar symptoms. Fischer (2019) also reported a possible correlation between the presence of *Fmed* (but also other GTD related fungi) and leaf symptoms in rootstock mother plants. Ouadi *et al*. (2019) observed white rot on 15 to 50% of the total necrotic area of trunks and cordons in 16-year-old 'Cabernet Sauvignon' grapevines expressing foliar symptoms. Edwards *et al*. (2010), after fully dissecting trunks of ten GLSD symptomatic vines (aged 4 to 7 years) detected white rot in only one vine. Mugnai *et al*. (2010) dissected nine symptomatic 5- and 6-years-old vines. They found that four of the vines had no white rot and five had traces of decayed wood, mainly following infections from desuckering wounds (Mugnai *et al*., 2010). These results confirm that white rot, and *Fmed* as the main white rot agent in Europe, becomes increasingly present as vines age, thus becoming increasingly associated with leaf symptoms. The pathogen may play a fundamental role in activating mechanisms leading to the onset of leaf stripe symptoms. However, observations of foliar symptoms not linked to white rot suggest that even if *Fmed* plays a very important role, other factors are also likely to be involved.

In 10-year-old 'Cabernet Sauvignon' cordons expressing foliar symptoms, Bruez *et al*. (2020) using meta-barcoding, proposed the link between the onset of GLSD with white rot and a combination of *Fmed*, *Pch* as well as *Sphingomonas* spp. and *Mycobacterium* spp. They suggested that microbiota interactions in white rot necrotic tissues could induce production of phytotoxic secondary metabolites, or increase some shared metabolic pathway, thereby inducing typical GLSD foliar symptoms. *In vitro* production of fungal secondary metabolites by co-culture with bacteria has been documented (Haidar *et al*., 2016), but occurrence in natural conditions is yet to be assessed.

Cholet *et al*. (2021) and Pacetti *et al*. (2021) have also shown the correlation of white rot with foliar stripe symptoms. Decay elimination (curettage, see below for details) drastically reduced GLSD symptoms during the years following curettage treatment, in 24-year-old 'Sauvignon Blanc' and in 14-year-old 'Cabernet Sauvignon' plants. Another interesting correlation between white rot and foliar symptoms came from the curative side: recently, Bruez *et al*. (2021) shown how after sodium arsenite treatment (see below for details), 25-year-old 'Gewürztraminer', 27-year-old 'Chardonnay' and 40-year-old 'Merlot' plants did not shown any foliar symptoms.

In conclusion, the relationship between outbreak of foliar symptoms and white rot in the Esca complex of diseases is widely supported and linked to *Fmed* in Europe, although this is not exclusive as the fungus is absent in young symptomatic vines. Nevertheless, clarifying the mechanisms involved in this relationship will be a big step towards full understanding of the processes leading to the characteristic symptoms and symptom expression timing of GLSD (the symptom fluctuations is not found in other diseases of perennial hosts). Several hypotheses have been proposed for etiology of leaf stripe symptoms, but to understand the role of *Fmed* in development of the disease, an important and essential first step is to detect the signals reaching the leaves and causing the outbreak of these symptoms. In the case of *Fmed* we suggest the following etiology: *i*) joint action of extracellular enzymes and toxins (from *Fmed* or the entire white rot microflora); *ii*) vascular system destruction caused by lignocellulolytic enzymes; *iii*) the formation of low molecular weight diffusible compounds from *Fmed* or from wood degradation-host infection reactions; and *iv*) a combination of these situations and the wood cellular microenvironment.

GENOMIC INFORMATION

Many fungal *Agaricomycetes* genomes have been sequenced by the Joint Genome Institute (JGI) (http://jgi.doe.gov/fungi) (Grigoriev IV *et al*., 2011). According to these data, 93% of the *Agaricomycotina* sequenced genomes are from *Agaricomycetes*. This could be related to the roles of these fungi in trees decay and to their potential applications in biotechnology (Lundel *et al*., 2014; Hyde *et al*., 2019). In a comparative genomic study, Floudas *et al*. (2012) sequenced the *Fmed* genome. The final draft assembly was obtained by *in silico* combination of Roche (454), Sanger Fosmids, and Illumina data. Information on genome annotation statistics and composition are available at the MycoCosm portal (https://mycocosm.jgi.doe.gov) (Grigoriev IV *et al*., 2014) and in Floudas *et al*. (2012).

Fmed genome size is approx. 63.35 Mbp which accounts for 11,333 predicted complete gene models with start and stop codons. The genome shows a conspicuous repetitive sequence component, mostly represented by microsatellites and Transposable Elements (TEs). It is

generally accepted that repetitive sequences play roles in *Basidiomycota* genome rearrangements and gene mutations, interrupting genome linearity between strains, and producing strain polymorphisms (Castanera *et al*., 2017). This could at least partially explain the level of polymorphism detected between strains of *Fmed* (Pollastro *et al*., 2001). Specifically, 4157 microsatellites were detected, most of them (52.27%) being dinucleotides, followed by tri-, mono-, penta-, hexa- and tetra-nucleotide microsatellites. TE analysis revealed a high proportion of TEs coverage (41.42%), representing the greatest for the sequenced genomes in the study. The biggest portion of TEs was LTR-Gypsy elements (21.33%), followed by LTR-Copia, TIR, DNA-transposons and Helitrons. A consistent number of non-classified TEs were reported (Floudas *et al*., 2012).

Besides constitutive analysis of the genome, Floudas *et al*. (2012) conducted a comparative study with 30 fungal genomes (presenting different ecological strategies), to establish the origin of ligninolytic activity. Through molecular clock analysis of genes encoding Class II Peroxidases (PODs: responsible for lignin degradation), it was possible to date the appearance of ligninolytic activity and the *Agaricomycetes* ancestor (a white rot agent, most likely). The activity probably appeared approx. 290 Ma ago (between the end of Carboniferous and Permian period, Paleozoic era). Subsequently, by Class II PODs-encoding gene expansion through the lineage, five orders of basidiomycetes differentiated, including the *Hymenochaetales* (most likely approx. 237 Ma, during the Triassic period, Mesozoic era). *Fmed* was estimated to have up to 17 Class II PODs-encoding genes in its genome, and these genes can possibly be found clustered with cellobiose dehydrogenase (CDH) encoding genes and other unclassified genes.

Other gene copy numbers expanded in the lineage during *Fmed* genome evolution, such as genes encoding for glycoside hydrolases (GH) families, Fe (III)-reducing glycopeptides (GLP), dye-decolourizing peroxidases (DyP) and laccases (Lac) (Floudas *et al*., 2012). A detailed report on carbohydrate active enzymes (Cazymes) and class II PODs is presented below.

PATHOGENICITY

In vivo white rot basidiomycete pathogenicity studies on grapevine have been rarely documented (Chiarappa, 1997; Larignon and Dubos, 1997; Sparapano *et al*., 2000a, 2000b, 2001a; Gatica *et al*., 2004; Laveau *et al*., 2009; Luque *et al*., 2009; Diaz *et al*., 2013; Akgül *et al*., 2015; Cloete *et al*., 2015b; Amarloo *et al*., 2020; Brown *et al*., 2020), but contrasting results to fulfil Koch's postulates were obtained, and the role of basidiomycetes as causes of grapevine foliar symptoms (GLSD) is not clear. Experiments have been conducted either on young or old grapevine plants, but very few of these studies used *Fmed* as inoculum (Larignon and Dubos, 1997; Sparapano *et al*., 2000a, 2000b, 2001a; Laveau *et al*., 2009; Luque *et al*., 2009; Akgül *et al*., 2015; Amarloo *et al*., 2020).

The first pathogenicity study on *F. punctatus* (probably *Fmed*) was conducted in France by Larignon and Dubos (1997) to determine the pathogen's role in wood decay. After fungus inoculation of healthy 'Cabernet Sauvignon' wooden blocks or rooted canes, they observed formation of typical white rot only in wooden blocks. As expected the fungus only colonised old wood.

Sparapano *et al*. (2000a), inoculating old vines and assessing wound-induced wood discolouration and white rot symptoms, found that inoculation with *F. punctata* (probably *Fmed*) produced the symptoms with different timing dependant on the cultivar, host plant age and portion inoculated. Specifically white rot formation tooks: *i)* approx. 6 months after inoculation for symptoms to occur in trunks, branches and spurs of 6-year-old 'Italia', and 9-year-old 'Matilde' plants; *ii*) 2 years after inoculation of 13-year-old 'Sangiovese' vines spurs and branches; or *iii*) 2 years after inoculation in 2-year-old rootstock Kober 5BB grafted with 'Italia'. No symptoms on leaves were induced. While *F. punctata* re-isolation was successful, no other wood degrading fungi were re-isolated. Sparapano *et al*. (2000a) concluded that *F. punctata* (probably *Fmed*) could act as a primary pathogen, and was able to colonize the grapevine woody tissues without other previous fungal infections when inoculated through wounds.

To gain details on the role of each fungus in "Esca disease", Sparapano *et al*. (2000b, 2001a) studied fungus-to-fungus and fungus-to-plant interactions, both *in vitro* and *in planta* co-inoculations. Sparapano *et al*. (2000b) showed *in vitro* competitive interaction of *F. punctata* (probably *Fmed*) with *P. chlamydospora* and antagonism between *P. aleophilum* (= *P. minimum*) and *F. punctata*. They also observed that each fungus could act as a primary pathogen by *in planta* inoculations. Moreover, the effect of *F. punctata* (probably *Fmed*) on the woody tissue of 'Italia' and 'Matilde' grapevines was limited by *P. aleophilum (= P. minimum)* but not by *P. chlamydospora*. Only *F. punctata* (probably *Fmed*) alone was able to induce white rot. This fungus was re-isolated, but no foliar symptoms were observed in the co-inoculation experiments. Besides confirming the fungus-to-fungus competitive and antagonistic interactions with *Pch* and *P. aleophilum* (= *P. minimum*), Sparapano *et al*. (2001a)

found that *F. punctata* causes wood discolouration followed by limited and localised white rot lesions within 3 years after single-inoculations or all possible co-inoculations, in 5-year-old 'Italia' and 9-year-old 'Matilde' vines, when they were inoculated in the spurs, spreading slightly more rapidly when trunks of plants were inoculated. Fungus re-isolation was always successful, and few foliar symptoms (even though not fully corresponding to the typical tiger stripe pattern) were observed after 2 to 3 years from inoculation in all the inoculation combinations. Non-inoculated plants (experimental controls) did not develop foliar symptoms.

The most recent study of *Fmed* pathogenicity was conducted by Amerloo *et al*. (2020). They inoculated *Fmed* mycelium on 2-year-old rooted grapevine 'Kolahdari' cutting under controlled greenhouse conditions, obtaining wood discolourations (but not white rot) 10 months after inoculation, confirming that white rot formed only on old wood. The proportion of *Fmed* re-isolation was approx. 60%, and no foliar symptoms were recorded. These results were in agreement with findings in rooted cuttings of 'Cabernet Sauvignon' (Laveau *et al*., 2009), 1-year-old 'Macabeo' and 'Tempranillo' plants grafted onto Richter 110 rootstock (Luque *et al*., 2009), and 1-year-old rooted plants of 'Sultana Seedless' (Akgül *et al*., 2015).

Data from pathogenicity tests of *Fmed* and grapevine are still too scarce for postulation of general concepts, especially considering that multiple factors could play a role in wood symptoms appearance (i.e. grapevine cultivar, age, trunk portion). However, the experimental evidence on ability of the pathogen to primarily colonize grapevine wood, and on relationships between white rot presence/amount and external foliar symptoms, require further investigation, especially considering contrasting results obtained from artificial inoculations versus the ones obtained from curative experiments (see above).

Host specificity should also be considered. *Fmed* isolates from different hosts have been used for pathogenicity tests on citrus trees (Elena *et al*., 2006). According to the extent of wood discolouration in citrus trees after inoculation with *Fmed* isolates from *Citrus*, *Vitis, or Actinidia*, a degree of host specificity for *Citrus* spp. was suggested. Other cross-pathogenicity tests conducted by Markakis *et al*. (2017) shown a certain degree of host-specificity in *Fmed*: grapevine-isolates inoculated in wood of pomegranate tree and kumquat tree shown shorter wood discoloration (and no fungal re-isolation) than in pathogenicity test with isolates from the same trees.

Study of host specificity for different *Fmed* isolates could elucidate dissemination modes for *Fmed*.

As indicated above, most wood and/or foliar vine symptoms could be caused by enzymes, toxins and/or other metabolites secreted by the pathogens individually or in combinations spreading through vines from the colonised wood, together with products of host defence reactions (Sparapano *et al*., 1998; Graniti *et al*., 1999; Mugnai *et al*., 1999; Amalfitano *et al*., 2000, 2011; Sparapano *et al*., 2000a, 2000b; Bruno and Sparapano, 2006b; Claverie *et al*., 2020). Recently, wood degradation in grapevine diseases was critically reviewed in comparison with other tree species by Schilling *et al*. (2021), reinforcing our observation that studying enzymatic and non-enzymatic fungal degradation, together with host defence related compounds, could be the key to understanding fungal adaptation to grapevine, and provide insights into wood and foliar symptoms.

Enzymes

White rot in wood is the result of lignin, cellulose, and hemicellulose degradation (either simultaneously or preferentially) by extracellular enzyme activity (Blanchette, 1991). These enzymes include: *i*) carbohydrate-active enzymes (CAZymes), such as endoglucanases (EC 3.2.14), cellobiohydrolases (EC 3.2.1.91, classified in the Glycoside Hydrolase family, GH), β-glucosidases (EC 3.2.1.21) and cellobiose dehydrogenase, CDH (EC 1.1.99.18); *ii*) laccases (EC 1.10.3.2; p-diphenol:di-oxygen oxidoreductases); and *iii*) Class II peroxidases (PODs), such as manganese peroxidases (MnP; EC 1.11.1.13), lignin peroxidases (LiP; EC1.11.1.14) and the versatile peroxidases (VPs, EC 1.11.1.16) (Daniel, 2014). Auxiliary activities (AA) redox enzymes are also considered to be present in white rot agents: eight families of ligninolytic enzymes and two of lytic polysaccharide mono-oxygenases (LPMOs) are associated with CAZymes and Class II PODs, since they may contribute jointly to degradation of polysaccharides (Levasseur *et al*., 2013; Daniel, 2014). Carbohydrate-Binding Modules (CBMs) are non-catalytic modules which were also found to be associated with CAZymes, contributing to polysaccharide degradation activity (Boraston *et al*., 2004). All these enzymes are currently collected for each fungus in the Carbohydrate Active Enzymes database (CAZy database, https://www.cazy.org), including its update for AA (http://www.cazy.org/Auxiliary-Activities.html) (Levasseur *et al*., 2013; Lombard *et al*., 2014).

Enzymes included in the pool of fungal secreted proteins, the secretome, can be involved in *Fmed* pathogenicity. *Fomitiporia mediterranea* and *F. punctata* (probably *Fmed*) secrete ligninolytic enzymes (such as laccases and peroxidases), and cellulolytic enzymes (such as endo-

1,4-β-glucanases and β-glucosidases), for which *in vitro* activities in *Fmed* cultures have been assessed (Mugnai *et al*., 1999; Bruno and Sparapano 2006a). Laccases are known for their oxidase activity on a large set of phenolic compounds, and on non-phenolic compounds in the presence of mediators (Pérez *et al*., 2002). However, the role of laccases in plant-pathogen interactions is still discussed. Their importance in pathogenicity has been suggested for some fungal species, such as the chestnut blight pathogen *Cryphonectria parasitica* (Murrill) M.E. Barr, through tannin detoxification and involvement in several other metabolic pathways, such as fungal morphogenesis and pathogenesis (Singh Arora and Kumar Sharma, 2010). For *Fmed*, Abou-Mansour *et al*. (2009) purified a typical fungal 60kDa laccase from some isolates. This enzyme oxidizes many natural polyphenolic compounds. Complete lignin degradation was not achieved alone, however, but only with the contributions from ligninolytic class II PODs. Three manganese peroxidase genes supplementing laccase activity were characterized in the *Fmed* genome, as *Fmmnp1, Fmmnp2* and *Fmmnp3* (Morgenstern *et al*., 2010). Cloete *et al*. (2015b) highlighted the LiP activity of *Fmed in vitro*. It therefore appears that *Fmed* produces a complete white rot-type enzymatic pool, capable of oxidizing and mineralizing lignin and polysaccharides. In addition, comparative genomic studies supported laboratory data and highlighted a rich enzymatic pool for *Fmed*. Floudas *et al*. (2012) and Riley *et al*. (2014) showed that *CDH* gene copies, several *GH* gene families, *LPMOs* and *CBM* family 1 (*CBM1*) genes were detected for the CAZymes pool. Other AAs were identified for lignin degradation pathways, including multicopper oxidases (MCO), copper radical oxidases (CRO), benzoquinone reductase, iron permease (FTR), and ferroxidase (Fet3) (Floudas *et al*., 2012). The genes encoding for the latter five proteins have been described as genes involved in the non-enzymatic wood degradation caused by some brown rot pathogens (Sista Kameshwar and Qin, 2020). This could support the hypothesis that a similar non-enzymatic iron-dependent system (as described by Goodell *et al*., 1997, for brown rot, and by Osti and Di Marco, 2010, for the *Pch* and *Pmin* soft rots) could also be part of the *Fmed* white rot process (Moretti *et al*., 2019). Low Molecular Weight Compounds (LMWC) Fe^{3+} reductants could also be involved in generating OH radicals through a mediated Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + {}^{-}OH$), as suggested in the Chelator Mediated Fenton (CMF) model proposed by Goodell *et al*. (1997). Three studies support this hypothesis, including: *i*) the *Fmed* draft genome revealed a homologous *SidA* gene responsible for inducing siderophore biosynthesis in *Ustilago maydis* (DC.) Corda (Mei *et al*., 1993; Floudas *et al*., 2012; Canessa and Larrondo, 2013); *ii*) *F. punctata* (probably *Fmed*) produces LMW metabolites *in vitro*, some of which have iron-chelating ability (Sparapano *et al*., 2000b; Di Marco *et al*., 2001); and *iii*) the *Fmed* genome includes genes codifying for reducing-polyketide synthase (R-PKS) which upregulate in some brown rot fungi, and these have been related to LMWC production likely involved in the redox chemistry of non-enzymatic degradation models (Goodell *et al*., 1997; Riley *et al*., 2014; Goodell, 2020). These observations are in line with Riley *et al*. (2014), who observed that the lignocellulolytic gene pathway does not capture the prevailing paradigm of white rot/brown rot wood decay fungi over several *Basidiomycota* genomes. A more nuanced and less dichotomic categorization of rot types could be implemented.

The *Fmed* genome also includes several gene copies codifying for terpene synthase (TS), cytochrome P450 monoxygenase (CytP450) and glutatione transferases (GSTs) (Floudas *et al*., 2012). Together with R-PKS, TS could confer competition advantages against other microorganisms through secondary metabolite production (Riley *et al*., 2014). CytP450 could also be involved in secondary metabolite production, and was originally described with GSTs as part of fungal xenomes, often associated with intracellular detoxification processes against lignin and other secondary metabolites synthesized by plants in reaction to fungus attack (Morel *et al*., 2013). This could confer the "primary" pathogen character reported by Sparapano *et al*. (2000a, 2001a).

Degradative enzymes (such as laccases, peroxidases and tannases) produced by *Fmed* could also degrade antimicrobial substances synthetized by host plants (tannic acid and resveratrol), playing putative roles in host-pathogen interactions. Moreover, detoxification enzymes such as phenol-oxidases and peroxidases were also detected in the contact zones of dual cultures with *Fmed* and *Pch* or *Fmed* and *Pmin*, suggesting detoxification activity by these enzymes against antimicrobial substances secreted by antagonistic fungi (Bruno and Sparapano, 2006a).

In conclusion, studying the complexity of the enzymatic pool, the secretome and xenome, together with possible presence of a non-enzymatic iron-dependent pathway, could provide further insight into *Fmed*-grapevine interactions and "Esca disease" symptomatology.

Phytotoxic compounds, organic acids, and other molecules

Toxin production and translocation to foliage via sap flow has been often proposed as the possible cause of "Esca disease" foliar symptoms (Claverie *et al*., 2020),

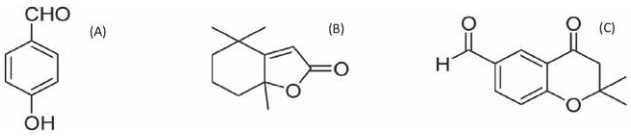

Figure 7. Phytotoxins produced by *Fomitiporia mediterranea*, based on relevant reports. (**A**), 4-Hydroxybenzaldehyde; (**B**), dihydroactinolide; (**C**), 6-Formyl-2,2-dimethyl-4-chromanone. Chemical formulae retrieved by PubChem (https://pubchem.ncbi.nlm.nih.gov/).

and its role in GTDs has recently been reviewed (Masi *et al*., 2018). It has been postulated that an oxidative burst triggered by the toxins in leaves could be more likely involved in foliar symptoms appearance than toxins themselves (Calzarano and Di Marco, 2018b). Toxicity thresholds and possible interference with other foliar susceptibility factors are still unclarified (Claverie *et al*., 2020). Production of low molecular weight metabolites with potential phytotoxicity was recorded (without identification) by Sparapano *et al*. (2000c), but phytotoxins were identified by Tabacchi *et al*. (2000) in *F. punctata* cultures (probably *Fmed*). They detected 4-hydroxybenzaldehyde, dihydroactinolide and 6-Formyl-2,2-dimethyl-4-chromanone (Figure 7), a phytotoxin related to eutypine produced by *Eutypa lata* (Deswarte *et al*., 1996a, 1996b; Andolfi *et al*., 2011). It was suggested that hydroxyl-benzaldehyde and its derivatives (carrying the aldehyde function) play important roles in the toxicity of fungi implicated in "Esca disease". Phytotoxicity was reported only for 4-Hydroxy-benzaldehyde on living protoplasts from *V. vinifera* 'Cabernet Sauvignon' at 10^{-5} and 10^{-6} M, as well as on callus from *V. vinifera* 'Gamay' grown in media supplemented with different concentrations of the metabolite (100, 250, and 500 mM) (Tabacchi *et al*., 2000). Further research is necessary to fully assess phytotoxicity of fungal metabolites and their roles in the diseases of Esca complex.

There is good correlation between fungus pathogenesis and oxalic acid secretion (Dutton and Evans, 1996). This is especially true for wood decay agents, where organic acids (mainly oxalic acid) may facilitate lignocellulosic biomass degradation, due to pH acidification, unstable and toxic divalent metal chelation, and H_2O_2 production (Kuan and Tien, 1993; Shimada *et al*., 1994; Tanaka *et al*., 1994; Urzúa *et al*., 1998). Oxalic acid metabolism is mainly regulated by two enzymes, i.e. oxalate decarboxylase (ODC, EC 4.1.1.2) and oxalate oxidase (OXO, EC 1.2.3.4), both of which catabolize the organic acid and reduce its level, which in high concentrations could be cytotoxic for pathogenic fungi (Svedružić *et al*., 2005; Zhuang *et al*., 2015). For *F. punctata* (probably *Fmed*), despite pH lowering in liquid culture (from 6.8 to 5.3; Sparapano *et al*., 2000c), Liaud *et al*. (2014) observed no organic acid production by *Fmed* in a comparative liquid culture chromatography screening. However, the presence of oxalate decarboxylase/oxidases gene copies in the *Fmed* genome (Floudas *et al*., 2012) indicates that epigenetic regulation of their expression could often occur.

Basidiomycete species are well known to produce pigments in response to abiotic and biotic stimuli, and these pigments act as chemical mediators during interactions between multiple organisms. Among them, terpene polyketide and amino acid derivates are known to be inducible, and to confer competition advantage (Spiteller, 2008, 2015; Halbwachs *et al*., 2016). In co-culture assays with *Hapalopilus rutilans* (Pers.) Murrill, *Fmed* mycelium increased pigmentation earlier compared to axenic culture, via hyperproduction of hypholomine B (Tauber *et al*., 2018), suggesting a role in interaction modulation. Interactions of *Fmed* with other microorganisms has been studied by Bruno and Sparapano (2006a) and Sparapano *et al*. (2000b, 2001b). In dual cultures with *Pmin* on modified Czapek medium, *Fmed* colony margins turned brown, became thicker and aerial hyphae formed ridge-like barriers, but the fungus growth stops at the contact zone. In dual cultures with *Pch*, after agonistic early growth, *Fmed* overgrew *Pch* mycelium (Sparapano *et al*., 2000b). The *Pmin* vs *F. punctata* (probably *Fmed*) antagonistic effect was confirmed in triple cultures with *Pch* in that condition, *Pch* was not overgrown by the *Fmed* mycelium, suggesting a suppressive role of *Pmin* (Sparapano *et al*., 2000b). Sparapano *et al*. (2001b) also studied the possible biochemical motivation of these agonistic and not-agonistic effects: *Pmin* and *Pch* culture filtrates, depending on their dilution in culture media, inhibited or reduced growth of *F. punctata* in Malt Extract Agar (ME). No inhibition of *Fmed* in ME medium was observed for *Pmin* or *Pch* crude organic extracts (ethyl acetate extraction of culture filtrates), purified scytalone from *Pmin* and *Pch* (at 1 mg mL^{-1}), pullulan from *Pch* (at 0.2 mg mL^{-1}) and oligosaccharides up to 2.5 kDa obtained by digestion of *Pch*-pullulan (2 mg mL^{-1}) (Sparapano *et al*., 2001b).

Study of the metabolome and transcriptome of the contact zones of different dual cultures to assess molecular cross-talking between *Fmed* and its competitor, would be worthwhile, to complete the partially studied secretome of this pathogen (Bruno and Sparapano, 2006a).

HOST PHYSIOLOGY CHANGES AND DEFENSE RESPONSES FOLLOWING *F. MEDITERRANEA* INFECTIONS

Data is sparse on changes in grapevine physiology and defence mechanisms specifically related to *Fmed*.

Effects of GTDs on grapevine physiology were reviewed by Fontaine *et al*. (2016b), but no specific responses to *Fmed* colonization and infection have been reported. Nevertheless, research on re-established plant vigour and quality grape production after 3 years from curettage treatments (see below) has demonstrated that white rot (where the main European decay agent *Fmed* is overabundant; Fischer and Kassemeyer, 2003; Bruez *et al*., 2017) probably affects grapevine physiology (Cholet *et al*., 2021). This follows observations by Ouadi *et al*. (2019) on 'Cabernet Sauvignon' plants presenting foliar symptoms of "Esca disease". They linked the abundance of necrotic wood (mainly white rot) in grapevine trunks and cordons with a 30% reduction in vine sap flow circulation, and thus leaf transpiration.

Few experiments have been performed to clarify plant defence mechanisms against *Fmed*. In callus/fungus dual culture experiments, Bruno and Sparapano (2006c) identified a number of phenolic molecules (benzaldehyde derivates, benzoic acid derivates, flavonols, flavonol-3-o glycosides, quercetin 3-rhamnoside, catechins and stilbenes) that were differentially induced in 'Matilde' and 'Italia' grapevines. Other studies have focused directly on vine sap (Bruno and Sparapano, 2006b, d) or brown-red symptomatic wood (Amalfitano *et al*., 2000, 2011; Agrelli *et al*., 2009) of "Esca disease"-symptomatic plants. Several stilbene-phenolic molecules were identified, which are theoretically toxic to *Fmed*, that showed greater sensitivity to phenols than *Pch* or *Pmin* (Amalfitano *et al*., 2001, 2011). Similar results were obtained by Rusjan *et al*. (2017) in wood of leaf stripe symptomatic vines, but with phenolic alterations reflecting both presence of the pathogen and wood condition in different parts of vines (trunks and rootstocks). Rusjan *et al*. (2017) proposed a relationship between the period of presence of the pathogen in different vine portions and their phenolic profiles. However, biomolecule concentration increases observed by Rusjan *et al*. (2017) may not be related exclusively to *Fmed*. Diseased plants are naturally infected by all the "Esca disease"-related fungi (*Pch, Pmin*, *Fmed*), and other possible microbial consortia highlighted by metagenomic approaches. Nevertheless, because a *Fmed-Pch-Pmin* interaction has been demonstrated, a relationship is likely between those compounds and *Fmed* (Sparapano *et al*., 2001b; Bruez *et al*., 2020). For this reason, results from most metabolomic studies in leaves responding to "Esca disease"-associated pathogens should be treated with caution, when attempting to understand exact plant responses to *Fmed* (Goufo *et al*., 2019; Moret *et al*., 2021). Further studies are necessary to precisely determine grapevine metabolite production burst specifically in response to *Fmed* colonization.

Damage to host hydraulic systems caused by the white rot necrosis could be the most important driver of physiological effects in grapevies, but specific studies are necessary to verify these hypotheses. To the best of our knowledge there have been no reported studies of wood compartmentalization specifically towards *Fmed*. The metabolic changes induced by *Fmed in planta* could generate biochemical markers for presence of the pathogen and wood degrading activity.

CONTROL STRATEGIES WITH A FOCUS ON *F. MEDITERRANEA*

Effective disease management is a major challenge in crop protection, and particularly for disease complexes such as "Esca disease". Efficiency of individual control methods for Esca complex of diseases is limited, and is best managed using integrated disease management, from nursery to vineyard. This includes cultural or remedial practices, vineyard sanitation, and use of pesticide chemicals or biological agents to protect grapevine wounds from pathogen infections (Gramaje *et al*., 2018). Methods to reduce or limit disease incidence, especially against *Fmed* infection, are outlined below.

Disease resistance

Incidence of "Esca disease" symptoms have been reported as cultivar-, rootstock-, and clone-related (Marchi 2001; Fussler *et al*., 2008; Grosman, 2008; Murolo and Romanazzi, 2014; Guan *et al*., 2016; Kraus *et al*., 2019; Moret *et al*., 2019), but they were all related to reduced presence of leaf symptoms, not to wood decay development. Some hypotheses could explain cultivar differences. Rolshausen *et al*. (2008) reported greater lignin levels in 'Merlot' grapevines tolerant to *E. lata* compared to susceptible 'Cabernet-Sauvignon' vines. A similar correlation has been suggested for *Fmed* affecting different olive tree varieties (Markakis *et al*., 2019). Assessment of susceptibility of wild grapevine (*V. vinifera* subsp. *sylvestris*) to *Fmed* could be worthwhile, because this host has been shown to be a promising potential source of resistance to Botryosphaeria dieback (Guan *et al*., 2016). Some data are available on other *Vitis* genotypes used in resistance source trials (Kraus *et al*., 2019). Fischer (2019) also detected regular presence of *Fmed* vegetative mycelium in rootstock mother blocks of rootstocks SO4, 5BB and 125AA in Germany, all of which were a cross population of *Vitis berlandieri* × *Vitis rupestris*.

Grapevine propagation material

The use of a good quality pathogen-free plant material is essential to limit inoculum propagation. Although *Fmed* has been shown to be present in blocks of rootstock mother vines (Fischer, 2009, 2019), and thus the derived plant material could be infected by "Esca disease"-associated fungi before nursery stages or during the propagation processes, *Fmed* has never been isolated from grafted 1-year old cuttings or propagation material. Furthermore, this pathogen has not been reported in grapevine nurseries (Larignon and Dubos 2000; Halleen *et al*., 2003; Zanzotto et al., 2007; Larignon *et al*., 2008a; Aroca et al, 2010; Gramaje and Armengol, 2011; Fischer, personal communication).

Protective and curative disease control methods

Curative control

Removing white rot from diseased grapevines seems to be efficient for reducing leaf stripe symptoms. This old technique, called "curettage" or "trunk surgery", consists of cutting affected vines and removing white rot with small precision chain saws. It provides good results; foliar symptoms are reduced even several years after curetting (Thibault, 2015). Cholet *et al*. (2021) demonstrated how curettage in "Esca disease"-symptomatic plants reduced foliar symptoms during 3 years after treatment, and re-establish vine vigour and grape production. Pacetti *et al*. (2021) confirmed foliar symptom remission in 14-year-old GLSD symptomatic 'Cabernet Sauvignon' vines for the following 2 years after complete trunk surgery, and demonstrated microbiome change induced by the treatment. *Fomitiporia mediterranea* abundance decreased after curettage, in parallel to an alpha-diversity increase in fungal population, suggesting a microbiota shift as a likely explanation for foliar symptom reduction during the post-curettage period.

Plant endotherapy is another promising curative technique against white rot. This includes direct treatment of white rot by drilling a vertical hole in grapevine trunks and injecting specific molecule solutions (typically fungicides), aiming to reduce foliar symptoms. However, due to the complexity of microbial consortia in diseased trunks, and because of the wood peculiar structure in old cultivated vines, specificity of the technique against *Fmed* needs to be refined. This approach is the subject of ongoing research (Gellon *et al*., 2017; Pacetti *et al*., 2019).

Sodium arsenite has been used in viticulture for a long time as the only effective and curative treatment against "Esca disease" (Songy *et al*., 2019b), and studies on modes of action of this compound are increasing. Larignon *et al*. (2008b) suggested *Fmed* as the most sodium arsenite sensitive "Esca disease"-associated fungus, and when Goddard *et al*. (2017) investigated the fate of arsenite within "Esca-diseased" treated plants, they found it concentrated in white rot necroses. Bruez *et al*. (2017) demonstrated that *Fmed* isolations were reduced from white rot necrotic tissue coming from sodium arsenite treated plants. Bruez *et al*. (2021) showed how in sodium arsenite treated 'Gewürztraminer', 'Chardonnay' and 'Merlot' vines (25 to 40 years old) expressing tiger stripe symptoms, the relative abundance of *Fmed* decreased in white rot necroses and necrosis boundaries, confirming *Fmed* as the most sodium arsenite sensitive among GTDs-associated fungi (Larignon *et al*., 2008b). Previously foliar symptomatic plants did not express these symptoms after treatment, suggesting that the positive effect of sodium arsenite on GLSD was from specific toxicity to *Fmed* in white rot necrotic tissues and their boundaries, where other parasitic and saprobic fungi (*Inonotus hispidus* Bull. P. Karst., *Lepiota brunneoincarnata* Chodat & C. Martín) took place, increasing their relative abundance (Bruez *et al*., 2021).

Except for host endotherapy, for which experiments are ongoing, up to now curettage is likely to be the most sustainable physical management method against *Fmed*. More user- and environmentally-friendly chemical curative alternative should be proposed. The long-term efficacy of curative treatments has not been fully assessed. Data on reduction of foliar stripe symptoms provided by these two curative techniques (curettage and sodium arsenite) reinforce the link between GLSD and white rot, suggesting that more studies are required on these disease management approaches.

Preventive control

Protection of grapevine pruning wounds is an essential point to reduce pathogen entry (Eskalen and Gubler, 2001; Eskalen *et al*., 2007). In some European countries, some pesticide products (based on boscalid or pyraclostrobin) and biocontrol products (based on specific strains of *Trichoderma* spp.) are available for protection against GTDs. However, research with these products for management of *Fmed* diseases has not been reported yet.

Beside the authorized and registered products containing boscalid, pyraclostrobin or *Trichoderma* spp., many products or molecules have been tested *in vitro* for the control of GTD pathogens, and these were reviewed by Gramaje *et al*. (2018) and Mondello *et al*. (2018b). For *Fmed*, however, only few reports are available. Chitosan

in *in vitro* tests gave a low EC_{50} value (1.53 mg L^{-1}) for *Fmed* (Nascimento *et al*., 2007). Sensitivity of *Fomitiporia* spp. to chitosan was first reported by Bruno *et al*. (2001). Incorporation of resveratrol in culture media gave a direct antifungal effect against *Fmed* growth (Mazzullo *et al*., 2000). Copper oxychloride and gluconate formulations slightly reduced *Fmed* mycelium growth *in vitro*, with an EC_{50} of 11.242 mg Cu L^{-1} (Di Marco *et al*., 2011). For biological control, sensitivity of *Fmed* to crude protein extracts (CPE) from *Bacillus amiloliquefaciens* AG1 has been recorded as 2.000 AU mL^{-1} (Alfonzo *et al*., 2012). Del Frari *et al*. (2019b) demonstrated with *in vitro* dual culture plates that growth of *Fmed* and other "Esca disease"-associated fungi was inhibited by *Epicoccum* spp., a member of ascomycetes which have been commonly identified in grapevine microbiomes. No clear data have been provided about effects of *Trichoderma* spp. on *Fmed*, in contrast to documented effects of these fungi on the growth of *Pch* and *E. lata* (Di Marco *et al*., 2004b; John *et al*., 2005).

CONCLUSIONS AND FUTURE PERSPECTIVES

We have made careful attempts to collect and review all relevant published information on *F. mediterranea*, to stimulate debate within the GTD scientific community. Approximately 20 years after formal classification of this fungus, it is well established that it induces white rot in the grapevine wood, but details of the relationships between *Fmed* and GLSD essentially remain unknown. The causes and biomolecular mechanisms of white rot, and their relationships with external grapevine foliar symptoms, has yet to be deciphered, especially in light of knowledge and observations reviewed here. To fully describe these processes could be a standing point in the context of GTDs, and will allow viticulture to adopt new solutions for management of grapevine trunk diseases.

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