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Review

Traditional and Emerging Approaches for Disease Management of *Plasmopara viticola*, Causal Agent of Downy Mildew of Grape

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Abstract: The oomycete *Plasmopara viticola*, which causes downy mildew, is currently one of the most destructive pathogens affecting grape production. Although native to the eastern United States, *P. viticola* was introduced into Europe in the mid-to-late 1800s and is now found in virtually every grape-growing region of the world. Since its discovery, much effort has been made to understand the life cycle and infection process of the pathogen to develop more effective management practices. Widespread application of fungicides, especially those which have only one mode of action, has led to an increased occurrence of resistance to these treatments. Thus, with increased fungicide resistance and rising environmental concerns surrounding their use, traditional chemical management practices have begun to fall out of favor. Newer approaches, from targeted breeding utilizing quantitative trait loci to biological control agents, are continually being investigated and adapted to limit the damage caused by downy mildew. This review summarizes the current knowledge of the pathogen and methods of its control and explores potential avenues for future research focused on hypovirulence and biological control agents.

Keywords: *Plasmopara viticola*; downy mildew; grape; *Vitis vinifera*; fungicide resistance

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1. Introduction

Humans have had a long, close relationship with the grape genus *Vitis*, with management and domestication of the important subspecies *V. vinifera* having begun in the South Caucasus as early as 18,000 BCE [1]. Today, grapes are regularly ranked among the top five fruit crops globally and production has continued to increase over the past five years [2]. The crop is used for a wide array of commercial commodities including oil, raisins, juice, table grapes, and, most recognizably, wine. Between 2021 and 2028, the global wine market alone is predicted to experience a compound annual growth rate of 4.3% and grow to a value of USD 456.76 billion, up from a market value of USD 340.23 billion in 2021 [3].

Since the mid-1800s, grape production has been negatively affected by numerous diseases and pests, of which, one of the most destructive and challenging to combat is downy mildew. This disease is caused by the oomycete, *Plasmopara viticola* (Berk. & M.A. Curtis) Berl. & De Toni, a filamentous eukaryote that superficially resembles a fungus. The pathogen, which is native to the United States (US) [4,5], is now a global threat to grape production [6]. *Plasmopara viticola* lives its entire life cycle in and around the grape vine, infecting green tissues such as leaves, bunches, and inflorescences, contributing to significant losses of yield [4,7].

Numerous approaches for management of downy mildew have been developed over the past 150 years. The discovery and development of fungicides began in the 1880s [8] and breeding for resistance began shortly thereafter. Since that time, additional management methods utilizing fungal, bacterial, and other biocontrol agents have been developed, with varying degrees of success in pathogen control. One of the most promising

approaches to management has been through the identification and breeding for specific quantitative trait loci (QTL) correlated with increased resistance [9–11]. Fungicides are often used in conjunction with resistant cultivars to secure a successful crop. However, there are increasing occurrences of *P. viticola* developing mutations that allow it to evade the identified QTLs and entire classes of fungicides, making the need for new methods of growth control urgent. In this review, we summarize current knowledge regarding the pathogen and its management practices and highlight areas in which more research is needed.

2. Identification and Invasion History

Plasmopara viticola is native to the eastern US, where five formae speciales, including f. sp. *aestivalis*, f. sp. *riparia*, f. sp. *vinifera*, f. sp. *vulpine*, and f. sp. *parthenocissus*, are known to occur on various Vitaceae species [5,12]. It has been reported that the pathogen was first identified in 1834 as *Botrytis cana* by Schweinitz [13–15]; however, the basionym recognized by Mycobank [16] and the US Department of Agriculture National Fungus Collections Fungal Databases [17] is *Botrytis viticola*, as identified by Berkley and Curtis in 1848. Although the species was officially identified by Berlese and De Toni in 1888 as *Plasmopara viticola*, it has been known by many synonyms including *Peronospora viticola* [18–20], *Phytophthora viticola* [20], *Rhysotheca viticola* [14,19,20], and *Plasmopara amurensis* [20,21].

The international spread of downy mildew was first noted in France in September 1878 [4], at approximately the same time the country began to import American rootstock to replant vineyards devastated by the *Phylloxera* infestation responsible for the Great French Wine Blight [5,7]. Until the early 1870s, France had maintained a ban on imports from the US; thus, while the *P. viticola* may have been introduced with vines imported for scientific purposes prior to the 1870s, it was likely the lifting of the ban and subsequent planting of 400,000 US cuttings by the winter of 1872 [22] that contributed to its rapid spread. Within a few years, the occurrence of downy mildew had been reported in wine growing regions throughout Europe [4]. At the time, there was some debate whether the disease was native to Europe, because there were reports of molds producing similar symptomology in Germany and Switzerland [4]. Viala [4] disagreed, asserting that evidence supported its introduction from the US. Recent DNA sequencing supports Viala's assertion and demonstrated that the introduction involved a single cryptic species, *P. viticola* f. sp. *aestivalis* [5].

Following its introduction to Europe, the disease spread across the globe. The 2021 study by Fontaine et al. [5] suggests that rather than spreading through the direct importation of diseased plant tissue from the US, it was primarily the movement of infected tissue out of France and into China, South Africa, Australia, and Argentina that introduced downy mildew to the developing wine-producing regions. Today, it continues to be identified in new regions and affecting new species [23] and has been documented or reported in 96 countries and found on every continent except Antarctica [6].

3. Pathogen Life Cycle

As a biotroph and obligate host-specific parasite, *P. viticola* requires the living, green tissue of *Vitis* spp. (grapevine) to complete its life cycle, and as an oomycete lacking cell walls, it requires moist conditions to survive and reproduce on and around the vine. Inoculum for the primary infection of the grapevine is produced by oospores, the product of sexual reproduction [24,25]. In the spring, oospores that have overwintered in plant litter and soil germinate once conditions become favorable. Temperatures of 10 °C or greater and wet conditions promote the development of oospores into microsporangia [7,24], from which biflagellate motile asexual zoospores are released (Figure 1). Because oospores can survive for several years on litter, this process can occur repeatedly throughout the growing season, as long as conditions are favorable for germination [25].

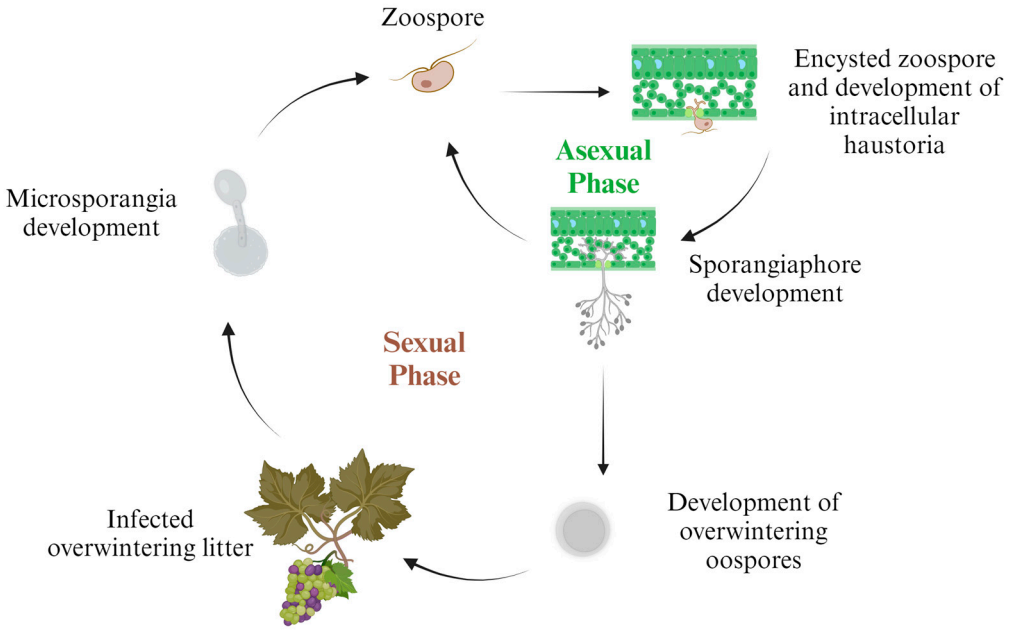

Figure 1. *Plasmopara viticola* disease cycle. Image generated in BioRender.

Released zoospores reach developing grapevine tissues via rain splash and dew accumulation, after which they encyst in the tissue and form a germ tube (Figure 1) [7,25]. This tube enters green stems and leaves through stomatal openings, and the pathogen intercellularly colonizes the host tissue for a period of several days [7,25]. During this time, *P. viticola* produces intracellular haustoria (Figure 1), with which it extracts nutrients from the host plant [25,26]. If optimal conditions of high humidity and temperatures between 15 °C and 25 °C exist, the intercellular mycelia will begin to produce sporangiophores (Figure 1) approximately one week after the initial infection occurred [25,27,28]. During the period from infection to the production of sporangiophores, no symptoms will be visible. Following sporangiophore formation, the undersides of the leaves will exhibit visible white "downy" symptoms and zoospores will be released via rain splash or wind dispersal, which promotes the secondary infection of leaves, stems, flowers, and berries. As with the release of zoospores from microsporangia beneath the vine, this stage can also occur repeatedly throughout a growing season. There is also evidence to suggest that the nighttime temperature can affect the progression of the disease, with warmer temperatures (25 °C) resulting in accelerated growth and sporulation compared to cooler temperatures (15 °C) [29]. In a controlled study of two *P. viticola* cryptic species, temperature was observed to have a significant effect on the aggressiveness of the pathogen, and aggressiveness differed between the species evaluated [28]. Thus, when warm temperatures and high humidity are sustained, the infection cycle can progress more rapidly and will be compounded by the presence of both sexual and asexual spores.

As the growing season for the grapevine ends and conditions become drier, *P. viticola* shifts from asexual to sexual reproduction [7,25] (Figure 1). While the asexual phase of the life cycle is well described, less is known about the sexual phase. Importantly, it is this phase which contributes to genetic diversity within the species, though it may be uncommon or practically non-existent in regions with warmer climates [30,31]. Because the pathogen is heterothallic, differing and compatible mating types must be present for this stage of reproduction to occur [32,33]. A single diploid oospore develops from the fusion of haploid nuclei originating from the antheridium and oogonium of the compatible mating types. Following development, the oospore requires a maturation, or dormancy, period before it can germinate and begin the infection process all over again [34]. This maturation period appears to be governed by average and cumulative temperature values and by cumulative rainfall; in field conditions, oospores complete maturation prior to dormancy cessation of the grapevine [35]. Progression to the post-maturation period just

before the end of grapevine dormancy promotes germination of the microsporangia at the time of bud burst and leaf development [35]. This phase of the life cycle is the most critical, as it provides the initial inoculum for seasonal infection. Due to their lack of cell walls, asexual spores cannot survive the dormancy period from fall until bud burst in the spring. For this reason, identification of methods that can be utilized to either disrupt sexual reproduction in the fall or limit microsporangia sporulation in the spring are greatly needed to reduce the available inoculum and control infection occurrence in regions where sexual reproduction occurs.

4. Symptoms and Agricultural Consequences

Infection of leaf tissue results in diminished chlorophyll fluorescence as early as 4–5 days after infection is initiated, several days before any visible symptoms arise [36,37]. In resistant cultivars, which exhibit hypersensitive reactions, this results in a more rapid reduction of the photosynthetic rate than in susceptible cultivars, with susceptible cultivars exhibiting a reduction only after visible symptoms have appeared [37]. Resistant cultivars also exhibit stomatal closure and decreased transpiration as early as four days after inoculation [37], as well as increased production of anthocyanin-like compounds [38]. Increased production of H_2O_2 has been observed within hours of inoculation and continuing for up to 3 days afterward in resistant cultivars [39,40]; this was correlated with earlier development of necrotic lesions [39]. Such lesions are the first visible indications of *P. viticola* infection and typically appear as pale green-to-yellow "oily" spots on the surfaces of the leaves (Figure 2a). These spots can expand to affect much of the surface of the leaves, particularly in cultivars that exhibit hypersensitive reactions [38], which can lead to premature defoliation in severely affected vines. Reduced photosynthetic rates and premature defoliation can negatively affect sugar accumulation in berries and overwintering buds, as well as delay berry ripening.

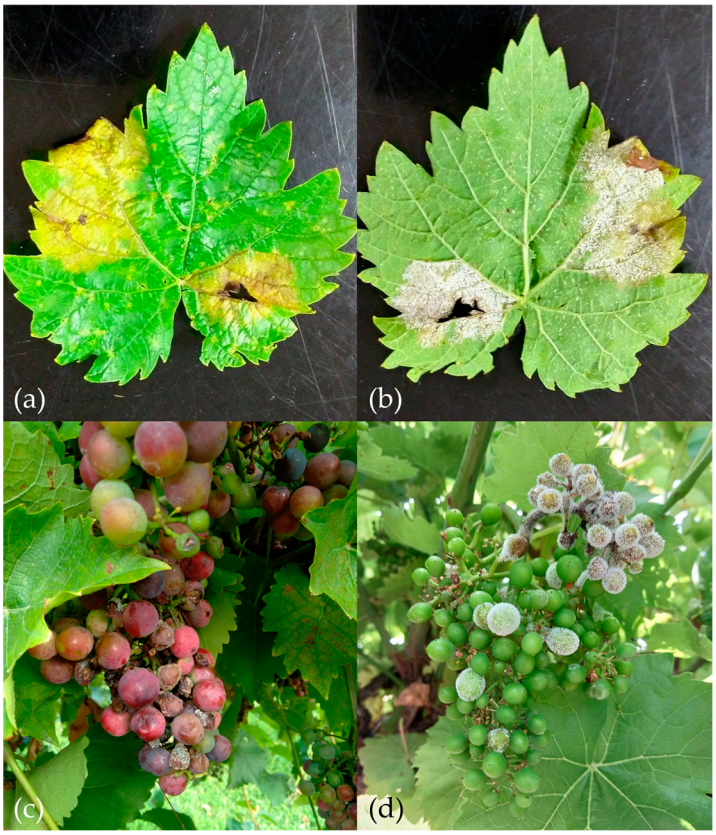

Figure 2. Symptoms of *Plasmopara viticola* infection. Oil spots on the surface of a Vidal leaf (**a**), fungal development on bottom of Vidal leaf exhibiting oil spots (**b**), shrunken and mottled berries of Chancellor (**c**), and sporulation on Chancellor berry surfaces (**d**).

When conditions are favorable, a white downy fungal growth develops on the undersides of leaves (Figure 2b). This is the primary source of inoculum for infection of inflorescence and young berries. Recent evidence has suggested that the disease may also spread systemically through the development of fan-shaped hyphae that can overcome physical barriers in susceptible cultivars and have been observed in young and nearly ripe berries [40]. In susceptible cultivars, infection of inflorescences at the time of swelling can lead to complete necrosis and loss of the bunch, while infection at the time of flowering can lead to partial necrosis and desiccation of bunch branches [41]. Young berries that become infected often halt development, exhibit brown mottling of the skin, and become necrotic (Figure 2c) and covered in a fuzzy white growth (Figure 2d) as the berries become filled with mycelia [40,41]. Some berries may continue to develop into what are known as "leather berries". These are brown, shrunken, dehydrated berries that were infected during early berry development [41] but continued to mature and develop seeds [40]. One study found that the seeds of leather berries contained no embryo or endosperm and were partially to completely infected with pathogen mycelia [40]. The resistance of berry tissue increases as stomata are converted into lenticels approximately two-to-three weeks post bloom [24]. However, the pedicle is susceptible up to four weeks post-bloom and infection can spread from rachis and pedicle to berries, even after berries are no longer susceptible to external inoculum [24]. Infection of leaves, flowers, and berries can be both qualitatively and quantitatively damaging to the final crop, as the sugar content is reduced and yield is lost. Although Fröbel and Zyprian [40] demonstrated that the pathogen can develop specialized hyphae to overcome barriers within the plant, it remains unknown whether the disease can spread from the bunches to the vine. To the authors' knowledge, no studies have yet observed transmission of the disease from rachis to cane.

5. Management Strategies

5.1. Cultural Practices

The effective management of downy mildew begins with best cultural practices, which include proactive methods such as site selection, varietal selection, vineyard sanitation, and vine care. Sites should have good airflow and be exposed to the sun for most of the day to promote rapid drying after rainfall. Additionally, sites should not be located near inoculum sources such as wild, feral, or abandoned grapevines [42]. Eradication of these secondary inoculum sources should help to reduce disease pressure [42]. Good sanitation measures such as removal of leaf debris after leaf fall, chopping up leaves, or tilling debris under can reduce inoculum in the vineyard. Mulching under grapevines can reduce the movement of primary zoospores from the soil to susceptible shoots [42], as can the removal of, or herbicide application to, suckers and ground-level growth that is susceptible to infection from the overwintering oospores [42]. New technologies are being explored to reduce chemical applications by increasing the accuracy of the targeting and identification of suckers for chemical spray removal utilizing two-dimensional laser scanners and camera machine vision [43]. Summer pruning promotes airflow and the quick drying of leaves, inflorescences, and clusters, as well as increasing fungicide spray penetration and coverage. This can be further supported by the use of trellis systems, such as vertical shoot position trellis systems, that promote high shoot growth and help keep leaves further away from inoculum in the soil [44]. The planting of grapevine varieties more resistant to downy mildew can reduce the number of fungicide sprays needed for downy mildew control [45].

5.2. Chemical Control

Even when planting resistant cultivars and using best cultural practices, chemical controls are still necessary to provide effective control of downy mildew, especially in seasons or regions where warm, humid, and rainy conditions persist [25]. The percentage of grapevine yields attributable to fungicide use is estimated to be 95% [46]. In warm humid climates, such as on the east coast of the US, downy mildew is normally treated with seven or eight fungicide sprays per season [47]. Early detection of downy mildew symptoms is

important for the timely application of chemical controls or other management strategies. Many advances in modeling and detection technologies have occurred in recent years, giving growers options beyond traditional scouting. Some of these technologies utilize thermal imagining, hyperspectral imaging, and artificial intelligence [38,48–52]. Such tools can support a more targeted approach to disease detections and fungicide application. Fungicide treatment options generally fall into two categories, contact or systemic, each with their advantages and disadvantages.

5.2.1. Contact Fungicides

The first chemical fungicide to control downy mildew is still effective today: the Bordeaux mixture, copper sulfate ($CuSO_4$) and lime [$Ca(OH)_2$] in solution. Millardet [8], in 1882, sprayed this mixture on grapevines close to the road to discourage people from eating his grapes, since it left a visible residue as well as tasted repugnant. He observed that treated vines did not have downy mildew symptoms, while the rest of the vineyard did [7,8,25]. Not long after, in 1887, the Burgundy mixture became available. It was similar to the Bordeaux mixture except that the copper sulfate was in solution with sodium carbonate (Na_2CO_3) instead of lime [7]. Fixed copper fungicides (copper oxychloride sulfate, copper hydroxide, copper sulfate) are used for multiple applications per season for effective control [7,25], despite the negative effects of excess copper in soils. Copper does not degrade in soil but accumulates, resulting in potential water and soil contamination that can be harmful to organisms [53,54]. As a result, the European Union has restricted the application of cupric fungicides (Regulation 473/2002) [53,55]. The microencapsulation of copper may offer a means of reducing the amount of copper applied per spray by up to 50% [53]. Another promising method to reduce copper inputs is by using biomimetic synthetic hydroxyapatite (HA) to improve the biological activity of copper ions [56]. Reducing or eliminating copper fungicides is a significant goal in developing new, sustainable methods for the management of downy mildew.

In the 1940s and 1950s, acuprics, also known as contact fungicides, were developed that provide comparable control to cupric fungicides. Many of these had multi-site activity that reduced the risk of resistance development [57]. These included captan (dithiocarbamates), methiram, maneb, mancozeb, propineb, captafol, folpet, and dichlofluanid [7,55]. The disadvantages of contact fungicides are that they sit on the waxy surface of the leaf, are subject to wash-off by rainfall, and only protect vines from future infections. They do not necessarily affect the haustoria of the *P. viticola* within the leaf or protect new shoot and leaf growth that occurs after application [25,58].

5.2.2. Systemic Fungicides

Fungicides that could penetrate the leaf's surface, allowing them to attack existing infections as well as provide lasting protection that could extend to new growth, occurred with the development of systemic fungicides in the 1970s and beyond. These systemic fungicides could not be washed off once inside the plant and displayed significant curative effects [7,55]. Some systemic fungicides could migrate within the plant to protect new shoots and leaves up to one-to-two weeks post-application [7,58,59]. The disadvantage of systemic fungicides is that they often have only one mode of action, which may result in a higher risk of resistance development [57,58]. The major systemic fungicides currently utilized in the US are listed in Table 1 with their respective mode of action (MOA) and Fungicide Resistance Action Committee (FRAC) code.

5.2.3. Fungicide Resistance Development in *Plasmopara viticola*

In the 1970s, it became clear that the resistance of plant pathogens including *P. viticola* to fungicide treatments was a major threat to crop production. The development of resistance is an evolutionary process through which sensitive pathogen populations become resistant via the selection of resistant mutants when faced with fungicide applications [58]. Single-site MOA fungicides such as quinone outside inhibitors (QoI) and phenylamides (PAs) are at

high risk for resistance development, whereas fungicides with multi-site MOA fungicides have a low risk of resistance development [57]. Three of the main FRAC groups with resistance concerns are reviewed here. However, even FRAC groups that are considered low risk for resistance can still develop resistance. Regular monitoring for resistant isolates is an important step in resistance management.

Table 1. Fungicide Resistance Action Committee (FRAC) codes and modes of action for fungicides approved for use to control *Plasmopara viticola* in the US.

Class	Fungicide	FRAC Code	Mode of Action	Systemic Action and Properties	Reference
Cyanoacetamide-oxime	Cymoxanil	27	Unknown	Contact and local	[7]
Benzamide	Fluopicolide	43	Disrupts cytoskeleton spectrum-like proteins	Xylem systemic	[7,60]
Benzamide	Zoxamide	22	Inhibits tubulin polymerization	Systemic	[61]
Carboxylic acid amide	Benthiavalicarb	40	Inhibits cellulose synthase	Local, preventative	[62]
Carboxylic acid amide	Dimethomorth	40	Inhibits cellulose synthase	Systemic, long residual activity, protective, curative	[63]
Carboxylic acid amide	Iprovalicarb	40	Inhibits cellulose synthase	Systemic, eradicative, preventative	[7]
Carboxylic acid amide	Mandipropamid	40	Inhibits cellulose synthase	Translaminar, rainfast, curative	[64,65]
Phenylamide	Acylalanine metalaxyl	04	Inhibits rRNA polymerase	Acropetal systemic	[7,66]
Phenylamide	Oxadixyl	04	Inhibits rRNA polymerase	Systemic	[67]
Phosphonate	Fosetyl-AL (ethyl-phosphite), phosphorus acid and salts	P07	Induces plant defenses	Acropetal and basipetal systemic	[7,68]
Quinone inside Inhibitor	Cyazofamide	21	Inhibits mitochondrial respiration	Local	[69]
Quinone outside Inhibitor	Ametoctradin	45	Inhibits mitochondrial respiration	Rainfast, preventative	[70–72]
Quinone outside Inhibitor	Famoxadone	11	Inhibits mitochondrial respiration	Local	[73]
Quinone outside Inhibitor	Fenamidone	11	Inhibits mitochondrial respiration	Local, translaminar	[7,74]
Quinone outside Inhibitor	Strobilurins	11	Inhibits mitochondrial respiration	Varying (translaminar to acropetal)	[7,75]

The carboxylic acid amides (CAAs) are a common fungicide class used to combat downy mildew on grape populations. This class inhibits cellulose synthesis in oomycetes [76] and impedes the growth of germ tubes and hyphae in oomycetes, reducing infection [77]. CAA fungicides have three different chemical structure subclasses (cinnamic acid amides, valinamide carbamates, and mandelic acid amides). Dimethomorth, a cinnamic acid amide, was the first one to be introduced in 1988 [78]. *Plasmopara viticola* dimethomorph-resistant isolates were first claimed to exist in French vineyards in 1994, and resistance was confirmed in 2007 [79–81]. A single mutation in the *PvCesA3* nuclear gene, glycine on codon 1105 mutated into a serine (G1105S), was identified as contributing to the resistance of *P. viticola* to CAA fungicides. It is a recessive mutation, thus both copies of the gene must have the mutation to be resistant [77]. CAAs have been used in the US since the introduction of mandipropamid in 2008 and dimethomorph in 2009. The first report of CAA resistance in North America occurred in 2016 in Virginia [82]. The resistance risk is considered moderate and can be managed by applying resistance mitigation strategies including preventive use, applying CAA fungicides in a mixture with effective partners (multi-site or other non-cross resistant fungicides), limiting the number of applications per season to three or four, and alternation with fungicides with other modes of action [83].

Another popular class of fungicides to control downy mildew is the quinone outside inhibitors (QoIs, FRAC code 11), which include strobilurins, famoxadone, and fenamidone. QoIs include nine chemical groups all shown to be cross-resistant and at high risk for resistance development [84]. The strobilurins are based on derivatives from the Basidiomycete mushroom, *Strobilurus tenacellus*. QoIs act at the quinol outer binding site of the cytochrome bc1 complex and inhibit mitochondrial respiration by blocking the transfer of electrons across the membrane, resulting in reduced energy production [85,86]. However, mutations of the cytochrome b gene, including glycine to alanine at position 143 (G143A) and phenylalanine to leucine at position 129 (F129L), result in *P. viticola* resistance, with G143 being the most commonly occurring [87]. The first commercial QoIs, azoxystrobin and

kresoxim-methyl, appeared on the market in 1996, and there are now twenty QoI fungicides in use. QoI fungicides are best used protectively and not curatively, as once the pathogen is inside the leaf, QoIs do not have as much of an effect (Table 1) [88]. QoI-resistant *P. viticola* isolates were documented in several European countries in the early 2000s [89], and resistant *P. viticola* and *Erysiphe necator* isolates were documented in Virginia and adjacent regions in 2005 [90]. Low levels of *P. viticola* resistance were documented in the Lake Erie vineyards in 2009 and 2010 [91]. Despite New York growers limiting QoI fungicides to two applications a season and mixing with an unrelated fungicide, *P. viticola* resistance was widespread in New York by 2014 and QoI fungicides could no longer be relied upon for downy mildew control. Part of the reason for this widespread practical resistance of *P. viticola* to QoIs is that New York growers primarily chose to mix QoIs with boscalid, which is effective against *E. Nector* not *P. viticola* [92]. Early detection of resistant strains, combined with more aggressive resistance management practices, may delay resistance development. Unfortunately, in some regions, QoIs can no longer be used to effectively control downy mildew.

Phenylamides (PAs) are fungicides that specifically target oomycetes including downy mildew. PAs (FRAC code 4) have long-lasting preventative action, are systemic in plants, provide curative effects, and are very safe for crops, making them especially useful in controlling downy mildew [93]. PAs inhibit ribosomal RNA (rRNA) biosynthesis (polymerase complex I) in downy mildew [94] and interfere with multiple growth stages in oomycetes, including hyphal, sporangial, and haustorial growth [95]. In 1977, metalaxyl/mefenoxam was the first PA brought to market. The two other PAs in use are benalaxyl/kiralaxyl and oxadixyl. Resistance to PAs in *P. viticola* occurred within just a few years of introduction in France [93] and resulted from the solo use of metalaxyl. FRAC was established shortly after PA resistance was discovered, and they quickly set guidelines for PA resistance management, requiring PAs to be used in mixtures, as preventative rather than curative agents, and limiting the number of sprays per season [58]. Although efforts have been made to determine the gene(s) responsible for resistance, the exact site of the mutation(s) is not fully known [96,97].

5.3. Biological Controls and Natural Substances

Alternatives to the chemical controls for downy mildew typically work by directly affecting *P. viticola* or, more commonly, by inducing the grapevine's own resistance mechanisms to thwart infection, or a combination of both. There are two main types of plant resistance: systemic acquired resistance (SAR), facilitated by salicylic acid and pathogenesis-related (PR) proteins, and induced systemic resistance (ISR), facilitated by jasmonic acid. The alternatives can be inorganic compounds, organic chemical inducers, natural extracts, or biocontrol agents (BCAs) [98]. BCAs and natural substances, while very promising, often do not consistently perform as well as chemical controls but are very valuable when used instead of chemical controls during periods of low disease pressure or in combination or alternation with chemical controls. This reduces the risk of chemical fungicide resistance development as well as reducing the chemical fungicide inputs into vineyards [7,99].

5.3.1. Inorganic Compounds

Among inorganic compounds, only three provide control against downy mildew: copper, potassium bicarbonate, and silicon nanoparticles. Copper, in the form of copper sulfate or copper hydroxide, has been found to promote plant defenses including peroxidases (POXs), phenols, anthocyanins, and resveratrol. Additional plant defense responses to copper sulfate (phytoalexins *cis*- and *trans*-resveratrol, *cis*- and *trans-piceid*, and *cis*- and *trans*-ε-viniferine) are increased further when copper sulfate is combined with a treatment of chitosan oligomers [100].

Potassium bicarbonate was found to be effective against downy mildew but also displayed phytotoxic effects [101]. Combining potassium bicarbonate and lime sulfur

lowered disease incidence and severity to levels comparable to or better than copper hydroxide treatment [102].

Silica nanoparticles (SiNPs) are of growing interest to promote the efficacy of fungicide delivery. Even without the addition of pesticides, however, SiNPs have been shown to reduce downy mildew pressure in grapes [103]. In a recent study, field-grown Thompson Seedless grapevines infected with downy mildew treated at 150 ppm with SiNPs achieved a reduction of up to 81.5% in disease severity [103]. Several increases in plant defenses were noted, including the overexpression of the transcription factor jasmonate and ethylene-responsive factor 3 and the defense-related genes β-1,3-glucanase, peroxidase, pathogenesis-related-protein 1, chitinase, and stomatal closure [103]. Silicon sprays also increased the yield (23.7%) and shoot length (26.3%) per grapevine, consistent with silicon's foliar fertilizer properties [103].

5.3.2. Hypovirulence

An area in need of research for discovering new BCAs is hypovirulence, or the reduction in the disease-causing capability of phytopathogenic fungi due to infection by mycoviruses. Hypovirulence has been used with some success throughout Europe to reduce the damage to sweet chestnut (*Castanea sativa*) caused by *Cryphonectria parasitica*, though less success has been observed in the US, where greater genetic diversity of the disease exists [104,105]. Several studies have identified mycoviruses infecting and, in some cases, causing the hypovirulence of downy mildews in multiple crops. In sunflowers, the *Plasmopara halstedii* virus leads to hypovirulence effects by weakening the aggressiveness of the downy mildew pathogen [106]. Mycoviruses have also been found to infect *Bremia lactucae*, the causal agent of lettuce downy mildew [107], while 283 new RNA viruses were identified in downy-mildew-infected grape leaves from regions in Spain and Italy, some of which may be candidates for BCAs as mycoviruses [108]. Utilization of hypovirulence poses its own challenges, however, as transmission requires the anastomosis of the hyphae, which may be restricted due to vegetative incompatibility. This condition prevents transmission between strains that are too genetically distant or of incompatible mating types. Thus, the use of hypovirulence will likely be more challenging in regions with greater genetic diversity of the pathogen.

5.3.3. Fungal

Endophytic fungi, fungi that live within plants, are possible sources of inhibitory substances against downy mildew. They produce secondary metabolites that can protect host plants against various microorganisms via antibiosis, as well as induce lignification of cell walls [109]. At least fifteen endophytic fungi have been shown to inhibit *P. viticola* [25]. Those that have been shown to be most effective against downy mildew are discussed here.

Trichoderma harzianum T39 (Trichodex® commercial product) has been shown to reduce disease severity in numerous greenhouse trials by priming plant defenses, increasing the expression of defense-related genes, and inducing of protective enzymes, resulting in systemic resistance [110–114]. In greenhouse trials, combining *T. harzianum* application (48-72 h before *P. viticola* inoculation) with benzothiadiazole (BTH) applied 24 h before inoculation provided 83% disease reduction and demonstrated systemic activation of grapevine defenses [110]. Field trials of *T. harzianum* HL1 and HL5 have also shown reduced disease severity, increased POX activity (HL1), increased POX levels (HL5), and improved quality parameters for berries [115]. *T. harzianum,* grown on a potato dextrose medium using the chemical inducer potassium tartrate, was tested in field trials for two years and significantly reduced the disease severity (78.9%, 81.8%) and average stomatal area, while increasing the phenolic content, POX, polyphenol oxidase enzyme activity, growth parameters, and yield parameters [116]. In field trials comparing five BCAs (*Streptomyces viridosporus*, *S. violatus*, *Trichoderma harzianum*, *T. viride,* and *Saccharomyces cerevisiae*) and commercial systemic fungicides (Bellis, pyraclostrobin, and boscalid) against downy mildew, *S. viridosporus* and

T. harzianum achieved the maximum reduction of disease severity (67.3%), which was better than the commercial fungicide treatment [115].

The pre-treatment of grape leaves with symbiote *Saccharomyces cerevisiae* (brewer's yeast) increased hydrogen peroxide and the expression of the protein (β-1,3-gluconase) in the resistant cultivar Vostorg, while expression of stilbene synthase increased in the susceptible cultivar Muscat Blanc [117]. Both cultivars had significant reductions in downy mildew sporulation in leaf assays [117]. Extracts of this yeast are used in several commercial formulations, including Romeo® and K&A Oomisine®, as a resistance inducer against downy and powdery mildew. Romeo was tested in Italy and other European countries, mainly on vines against *Botrytis cinerea*, *P. viticola*, and *E. necator*; the results were comparable to other biorational compounds but not as good as conventional controls [118]. The leaves of potted greenhouse vines (cv. Italia), sprayed at 1-week intervals with cerevisane (a cell wall derivative of *S. cerevisiae*), were used for transcriptomic analysis [119]. Cerevisane caused an increase in the expression of several defense response genes and was effective against downy mildew sporulation [119].

Acremonium sclerotigenum and *Acremonium persicinum* (formerly thought to be *Acremonium byssoides*) are endophytic fungi that have demonstrated hyperparasitism on *P. viticola*. *A. persicinum* hyphae and conidia bridle sporangiophores and collapse sporangia [120]. Culture filtrates that include secondary metabolites also inhibit sporangial germination [120,121]. *A. persicinum* has been found to attack oospores and effectively cause degeneration, such that they never germinate [122], making this a potential candidate for the post-harvest or pre-bud burst control of downy mildew.

Ubiquitous endophytes, including members of the genera *Penicillium*, *Alternaria*, and *Fusarium,* have also shown potential for use as BCAs. A water-based mycelium extract of *Penicillium chrysogenum* provided varying levels of control for downy mildew in greenhouse and field trials due to non-fungicidal effects including the activation of plant defenses and induction of many resistance-related metabolites [123,124]. Leaf discs treated with the endophyte *Alternaria alternata*, caused damaging structural changes to *P. viticola* without close contact, including necrotic haustoria, abnormal vacuolization, and accumulation of an electron-dense material within the vacuoles [125]. Three diketopiperazines (DKPs), low molecular weight metabolites, extracted from *A. alternata* significantly reduced *P. viticola* sporulation in grapevine leaf disks and greenhouse plants; however, field testing is needed [125,126]. Five mycoparasitic fungi, *Fusarium delphinoides*, *F. brachygibbosum*, two strains of *F. pseudonygamai*, and an unidentified *Fusarium* species, were observed coiling around sporangiophores of *P. viticola* and inducing lysis and inhibiting sporangia production by more than 50% in the leaf disc assays [127,128]. Fusaric acid, a dominant metabolite of the five *Fusarium* strains, inhibited *P. viticola* sporangia production by more than 80% in leaf disc bioassays [129]. A cold-tolerant UV mutagenetic strain of *F. proliferatum* G6, designated 1505, produced radial growth two to three times that of the parent strain at desirable temperatures (13 °C) for *P. viticola,* despite *Fusarium* spp. normally preferring higher temperatures [130]. This aggressive growth resulted in greater inhibition of *P. viticola* in leaf disk assays than the parent strain. The culture filtrate of strain 1505 displayed much higher levels of extracellular β-glucosidase and *endo*-1,4-β-glucanase activity than strain G6 [130]. It is important to note, however, that members of these genera are plant pathogens in their own right and have been found to induce asthma and allergies in humans. Thus, consideration of their effect on unintended targets must be considered when developing fungistatic or fungicidal treatments from their derivatives.

Arbuscular mycorrhizal fungi (AMF) root colonization has been shown to enhance defense responses in the aerial parts of grapevine against *P. viticola*. AMF colonization led to the upregulation of genes involved in the stilbenoid biosynthesis pathway 48 h after *P. viticola* inoculation [131]. Higher amounts of stilbenoids (i.e., resveratrol, ε- and δ-viniferins, and pterostilbene) were present in AMF-colonized plants 10 days after *P. viticola* inoculation [131]. In separate studies, AMF-colonized grapevines had decreased expression of *P. viticola* effectors, specifically PvRxLR28, indicating that AMF-colonized grapevines

could hinder *P. viticola*'s ability to suppress plant defenses via effectors [132]. More research is needed to determine whether AMF has utility as a BCA or in an integrated pest management program.

5.3.4. Bacterial

Beneficial bacteria that inhabit the rhizo- and/or endosphere of grapevines may be able to be used as BCAs. The secondary metabolites of these bacteria may inhibit *P. viticola* by antibiosis, competing for nutrients, disrupting pathogen signaling, and promoting host plant defenses [99]. Recently, investigations into the phyllosphere bacteria that colonize grapevine leaves at varying concentrations throughout the grapevine's lifetime have led to promising results. In general, there was a correlation between the concentrations of phyllosphere bacteria and the grapevine's ability to thwart *P. viticola* infection [133]. Additional research is needed in this area to determine if phyllosphere bacteria could be used as BCAs.

Lysobacter capsici AZ78 can resist copper, allowing it to be combined with a low dose of a copper-based fungicide [134]. The prophylactic application of *L. capsici* AZ78 alone to grapevine leaves reduced downy mildew disease to the same degree as a copper-based fungicide [134]. A combination of *L. capsici* AZ78 and low-dose copper reduced downy mildew significantly better than full-dose copper treatments in greenhouse trials [134]. *L. capsici* AZ78 survives in the phyllosphere of grapevine plants and can withstand environmental stresses including starvation, freezing, mild heat shock, and UV light irradiation [134]. The use of formulation additives protected *L. capsici* AZ78 against environmental factors, particularly cool temperatures, and improved its longevity on the leaves greater than 10 times compared to additive-free formulations [135]. The degradation of *P. viticola* cell walls is likely due to the lytic enzymes and diketopiperazine metabolites produced by *L. capsici* AZ78 [25,136–138]. In large-scale field trials, *L. capsici* AZ78 was as effective as a reference fungicide (Kocide®2000) in controlling downy mildew on leaves and bunches and displayed low toxicity to non-target organisms [139]. Yeast population dynamics in fermenting musts and wine quality were also not affected by *L. capsici* AZ78 [139]. These promising greenhouse and field trails combined with *L. capsici* AZ78's ability to resist copper make it a very attractive BCA to be developed commercially.

The *Bacillus* genus has several promising BCA species. *Bacillus subtilis* KS1 was found to produce an antifungal lipopeptide, iturin A [25,140]. Cyclo (-L-Leu-L-Phe) (cLF), a diketopiperazine produced by *Bacillus subtilis* KS1, reduced both the disease severity and lesion density of downy mildew in grapevine growth chamber experiments by approximately 90% [141]. The DKP-induced plant defense responses included the expression of genes encoding chitinase and β-1,3-glucanase and the activation of the salicylic acid and jasmonate signaling pathways [141]. *Bacillus subtilis* and *B. pumilus* were tested in field trials for two successive years, and they exhibited strong preventive effects against *P. viticola* [142]. Confocal microscopy showed that both strains could recolonize grapevine leaves with some persistence [142]. *Bacillus subtilis* GLB191 supernatant was highly active against *P. viticola* in leaf disc assays due to both a direct effect against the pathogen and the induction of plant defenses (defense gene expression and callose production) caused by the fengycin and surfactin present in the supernatant [143]. The biofungicides Sonata (a.m. *Bacillus pumilus* QST 2808) and Serenade Aso (a.m. *Bacillus subtilis* QST 713) were tested in field experiments against downy mildew and displayed equal efficacy to each other, achieving 94% to 97% reduction in disease severity on leaves and a 100% reduction on bunches [144]. *B. pumilus* GLB197's whole genome was sequenced to better understand the molecular mechanism underlying the biocontrol of phytopathogens such as *P. viticola* [145].

Bacillus megaterium BMJBN02 obtained from soil can induce resistance via its salicylic acid content and the expression of pathogenesis-related genes [146]. In addition, field trials conducted over four growing seasons found BMJBN02 to be as effective at controlling *P. viticola* as the commercial fungicide nicotinyl morpholine at 0.1% [146].

Ochrobactrum sp. isolate SY286 reduced the disease severity in a detached leaf disc assay by 93% and showed control comparable to the fungicide Equation pro (famoxadone

and cymoxanil) and a metalaxyl–mancozeb combination in a 2-year field trial [147]. Scanning electron microscopy observations revealed damage to *P. viticola* mycelia and sporangia cell walls when subjected to a fermentation liquor of isolate SY286 [147].

5.3.5. Plant Extracts

Over fifty plant extracts have been identified that provide some control of downy mildew either on leaf discs, under greenhouse-controlled conditions, or field conditions. However, the high levels of control observed in these conditions are usually not replicable in field conditions due to low durability and rainfastness [25]. Koledenkova et al. [25] provides a comprehensive list of the plant extracts that have been researched, and Zanzotto and Morroni [98] provide detailed descriptions of many plant extracts and their efficacies. Here, we will discuss some of the more promising extracts, recent findings, and other plant derivatives.

Laminarin extracted from the brown seaweed *Laminaria digitata* elicits numerous plant defense mechanisms, including activating 10 defense-related genes, the production of resveratrol and epsilon-viniferin (phytoalexins), calcium influx, and oxidative burst [148]. Field trials conducted by Romanazzi et al. [149] revealed poor control against *P. viticola* when used alone but stronger results when combined with low doses of copper salts or *Saccharomyces* spp. extracts. Sulphated laminarin, PS3, is a highly effective resistance inducer that provides more effective resistance against downy mildew than laminarin alone [150]. When applied with the surfactant Dehscofix CO125 (DE), cuticular diffusion increased, leading to greater efficacy [151].

DL-3-aminobutyric acid (BABA), an SAR compound that has no known antifungal activity, provides significant systemic and local protection against downy mildew both preventatively and curatively by inducing the grapevine's own defense system [152–154]. Grapevine leaf discs treated with BABA after infection with *P. viticola* showed an 85–94% reduction in sporulation [152]. Similar results in leaf disc assays and seedlings were obtained by Hamiduzzaman et al. [154]. In field trials using two foliar sprays of BABA or a mixture of different fungicides at reduced rates and BABA, downy mildew was controlled by more than 90%, comparable to metalaxyl-Cu or dimethomorph with mancozeb treatments [155]. Research on formulating BABA for commercial use while maintaining efficacy in field trials seems to be needed.

Chitosan, a natural polymer obtained from deacetylated chitin, reduced downy mildew infection on grapevine leaves and induced plant defenses, including the production of phytoalexins, resveratrol and its derivatives, epsilon-viniferin and piceid, and stimulation of chitinase and glucanase activity [100]. Field testing of chitosan showed an average reduction in downy mildew disease severity by 30% [156]. Combining chitosan with *Trichoderma* sp., *T. koningiopsis*, and a reduced rate of copper significantly reduced downy mildew severity on greenhouse plants, providing a possible means of reducing copper inputs [157]. Further testing will be needed to demonstrate true efficacy under field conditions.

Several extracts have shown near total suppression of downy mildew alone or in conjunction with additional phytocompounds. A 96% ethanolic extract from the leaves of *Inga sapindoides* offers greenhouse grapevine plantlets defense against downy mildew that is comparable to copper treatments [158]. At 0.5 mg/mL, this extract provided 96% or 97% reduction in downy mildew compared to a 100% reduction with the copper treatment [158]. A phytocomplex, derived from *Salvia officinalis* and containing rosmarinic acid (10.12% *w*/*w*), applied to grapevine leaf discs at 5 g/L that were then inoculated with *P. viticola*, inhibited sporulation by 95% compared to the control and was significantly better than the 77% inhibition by rosmarinic acid alone [159]. Five promising compounds were isolated from three *Larix* species: larixol, larixyl acetate, lariciresinol, lariciresinol acetate, and one from *Pinus sylvestris*, 7a,15-dihydroxydehydroabietic acid. These compounds showed 90% to 100% efficacy under semi-controlled greenhouse conditions against downy mildew [160].

Essential oils are attractive alternatives to chemical controls because they contain terpenes and terpeniods that have fungicidal activity and have been shown to disrupt cell membranes, cause cell death, and reduce the sporulation and germination of fungi [161,162]. Field testing is often lacking due to low durability and rainfastness [162]. The essential oil of *Origanum vulgare* (oregano) proved to be 95% effective at reducing downy mildew sporulation when applied by plant fumigation continuously for 24 h post-infection compared to untreated vines [162]. The transcriptomic data derived from leaf RNA extraction revealed that the oregano essential oil vapor treatment stimulated the plant's immune defenses including salicylic, jasmonic acid, and phytoalexin synthesis among others [162]. Another study on oregano essential oil vapor (OEOV) treatment both pre- and post-infection observed significantly reduced downy mildew sporulation [163]. It was argued that the OEOV treatment primed the innate immune system of the vine [163]. Secondary metabolism and pathogen recognition and response were identified as significantly affected by OEOV; however, these mechanisms appeared to be separate from stilbene expression and included pathways not yet elucidated [163].

Additional work with essential oils was conducted by Fialho et al. [164] to evaluate the effect of seven essential oils (cinnamon, eucalyptus globulus, marjoram, melaleuca, peppermint, oregano, and white thyme) on spore germination in vitro and in field conditions. All essential oils displayed fungistatic activity and reduced sporulation in varying degrees ranging from 15 to 65% in field conditions [164]. However, essential oils showed chemical instability at longer incubation times. The cinnamon and eucalyptus globulus essential oils were the most antifungal towards the downy mildew of those tested [164].

The volatile organic compound (VOC) linalool, found in downy-mildew-resistant leaves, shows promise as a signaling molecule for plant resistance induction. Downy-mildew-susceptible leaf discs treated with linalool exhibited reduced downy mildew severity and encouraged the deposition of callose at the site of infection [165]. Linalool-treated leaf discs also displayed upregulation of genes involved in the salicylic acid and jasmonic acid defense mechanisms [165]. Importantly, these plant extracts, essential oils, and VOCs are derived from renewable resources potentially available in large quantities, making them attractive and promising alternatives to conventional fungicides.

6. Breeding Resistant Cultivars

Breeding for resistance or tolerance is a method of selective breeding used to reduce the effects of biotic and abiotic stresses in crops. Ultimately, it seeks to develop offspring that inherit the increased tolerance of one parent and the desirable crop qualities of another. Breeding for resistance is often a costly and time-consuming process, however, as it generally requires several generations of crossing and backcrossing to produce the desired outcome. The use of QTL mapping allows breeders to link a phenotype with a genotype to identify the potential genes associated with a desired trait, as well as identify offspring that have inherited the trait, making QTL mapping a more targeted approach to breeding for resistance than traditional methods.

In grapes, QTL mapping has identified 33 putative "Resistance to *Plasmopara viticola*" (Rpv) loci in wild and cultivated species (Table 2). These loci have been observed to confer differing levels of resistance, ranging from weak to nearly complete resistance, and have been mapped to 15 of the 19 chromosomes, excluding chromosomes 1, 13, 17, and 19 (Table 2). Ten of the 33 Rpv-related QTLs have been identified on two chromosomes, chromosome 14 (Rpv8, Rpv12, Rpv19, Rpv29, Rpv32) and chromosome 18 (Rpv2, Rpv3, Rpv15, Rpv24, Rpv27). Three Rpvs each are found on chromosomes 7, 9, 12, and 15 and two are found on chromosome 5. This clearly illustrates that although resistance QTLs are most frequently found on chromosomes 14 and 18, loci correlated with resistance are found throughout the genome.

Table 2. Phenotypic variation explained by resistance to *Plasmopara viticola* (Rpv) loci identified from multiple *Vitaceae* species under varying infection settings.

Locus	LG	Species or Cultivar	Origin	Inoculation/Infection Setting	Explained Phenotypic Variation	Trait	Reference
Rpv1	12	*Muscadinia rotundifolia*	North America	-	73%	-	[9]
Rpv2	18	*Muscadinia rotundifolia*	North America	-	Total *	-	[166]
Rpv3	18	Regent	-	Field; greenhouse	37.3%	Leaf necrosis; berry cluster resistance; lesion size	[167]
Rpv3	18	Bianca	-	Field; greenhouse	33.9–80.5%	Leaf necrosis; mycelial growth; sporulation	[168]
Rpv3	18	*V. rupestris, V. labrusca x V. riparia*	North America	Laboratory	na	na	[169]
Rpv4	4	Regent	-	Field; greenhouse	22.6%	Leaf necrosis; berry/cluster resistance; lesion size	[167]
Rpv5	9	*V. riparia*	North America	Greenhouse	28.9–34.4%	Mycelial growth; sporulation	[170]
Rpv6	12	*V. riparia*	North America	Greenhouse	28.9–34.4%	Mycelial growth; sporulation	[170]
Rpv7	7	Bianca	-	Field; greenhouse	limited (not quantified)	Leaf necrosis; mycelial growth	[168]
Rpv8	14	*V. amurensis*	Asia	Greenhouse	36.0–66.5%	Leaf necrosis; sporulation	[171]
Rpv9	7	*V. riparia*	North America	Field; greenhouse	5.8–11.3%	Leaf necrosis; mycelial growth	[172]
Rpv10	9	*V. amurensis*	Asia	Laboratory	50.0%	Sporangiophore formation	[173]
Rpv11	5	Regent	-	Field; greenhouse	46.5–69.5%	Leaf necrosis; berry/cluster resistance; lesion size	[174]
Rpv11	5	Solaris	-	Laboratory	3.4%	Sporangiophore formation	[173]
Rpv12	14	*V. amurensis*	Asia	Field; greenhouse	74.5–78.7%	Leaf necrosis; sporulation	[10]
Rpv13	12	*V. riparia*	North America	Field; greenhouse	21.2%	Leaf necrosis	[172]
Rpv14	5	*V. cinerea*	North America	Field; laboratory	9.6–17.4%	Leaf necrosis; sporulation	[175]
Rpv15	18	*V. piasezkii*	Asia	-	-	-	[176]
Rpv16	-	-	-	-	-	-	[176]
Rpv17	8	*V. vinifera x V.* spp. (Horizon)	Asia x North America	Laboratory	12.94%	Leaf necrosis; sporulation	[177]
Rpv18	11	*V. vinifera x V.* spp. (Horizon)	Asia x North America	Laboratory	8.51–17.33%	Leaf necrosis; sporulation	[177]
Rpv19	14	*V. rupestris*	North America	Laboratory	11.83–15.51%	Leaf necrosis; sporulation	[177]
Rpv20	6	*V. vinifera x V.* spp.	Asia x North America	Laboratory	8.37%	Leaf necrosis; sporulation	[177]
Rpv21	7	*V. vinifera x V.* spp.	Asia x North America	Laboratory	10.90%	Leaf necrosis; sporulation	[177]
Rpv22	2	*V. amurensis*	Asia	Laboratory	26.4%	Leaf necrosis; sporulation	[178]
Rpv23	15	*V. amurensis*	Asia	Laboratory	26.2%	Leaf necrosis; sporulation	[178]
Rpv24	18	*V. amurensis*	Asia	Laboratory	30.0%	Leaf necrosis; sporulation	[178]
Rpv25	15	*V. amurensis*	Asia	Laboratory	Not quantified	Leaf necrosis; sporulation	[11]
Rpv26	15	*V. amurensis*	Asia	Laboratory	59.1–63.6%	Leaf necrosis; sporulation	[11]
Rpv27	18	*V. aestivalis*	North America	Field; laboratory	33.8%	Leaf necrosis; sporulation	[179]
Rpv28	10	*V. rupestris*	North America	Greenhouse; laboratory	24.3–66.5%	Sporangiophore formation	[180]
Rpv29	14	*V. vinifera*	Asia	Laboratory	Significant (not quantified)	Sporulation	[181]
Rpv30	3	*V. vinifera*	Asia	Laboratory	Significant (not quantified)	Sporulation	[181]
Rpv31	16	*V. vinifera*	Asia	Laboratory	Significant (not quantified)	Sporulation	[181]
Rpv32	14	*V. coignetiae*	Asia	Laboratory	36.4%	Not specified	[182]
Rpv33	9	*V. mustangensis x V. acerifolia* (PI 588149)	North America x North America	Field	47.7%	Leaf necrosis; sporulation	[183]

Information undescribed or unavailable (-), description derived from Blasi et al., 2011 (*)

The identified QTLs vary in terms of mapping stability, tissues exhibiting the strongest resistance, and the effect on the pathogen lifecycle. This variance is due in part to differences between the studies themselves regarding the cultivars and the tissues that were assessed, experimental conditions, and phenotyping of symptoms. Studies utilized field, greenhouse, and laboratory conditions (Table 2) to assess disease development on intact leaves [9,10,167,168,172,174,175,179,180,183], detached leaves [11], leaf discs [10,11,168,170,171,173–175,177–181], and berry clusters [167,174]. It is important to note that studies that involve detached grape tissue cannot evaluate the effect of polycyclic infections to identify the primary QTLs of sustained resistance, and more studies that investigate the genetics of cultivars exposed to repeated infection are needed. With the phenotypic variation explained by each Rpv ranging from 3.4 to 100% (Table 2), it is evident that resistance is complex and the degree to which a cultivar can suppress *P. viticola* infection likely depends upon the number and identity of the Rpvs present within the vine genome.

Several studies have evaluated the ability of individual loci to restrict pathogen growth and sporulation compared to stacked (multiple) loci within progeny, as stacking increases the number of times the pathogen must mutate to overcome resistance. These studies have found that progeny containing two or more loci exhibited an additive effect and increased levels of resistance [10,173,184,185], though there was variability within cultivars carrying the same alleles and stacking Rpvs may not necessarily result in sustained resistance [186]. In fact, there is already evidence of the breakdown of resistance conferred by several Rpvs (Rpv3, Rpv10, and Rpv 12) utilized throughout European vineyards [185,187]. Thus, careful consideration should be given when targeting loci for single or stacked breeding to reduce the occurrence of resistance breakdown.

7. Concluding Remarks

Plasmopara viticola is one of the most destructive pathogens affecting grape production today, and its management is of great importance. As the pathogen continues to develop mutations allowing it to evade modern chemical and breeding resistance mechanisms, the need to slow the rate of mutation occurrence and identify alternative approaches to management will increase. Continued research to elucidate the gene mutations that cause resistance is important for developing molecular tests to detect resistant isolates, as well as to understand how resistance develops. Regular testing for fungicide-resistant isolates is necessary to ensure resistance problems do not develop unnoticed but rather are addressed quickly by adjusting management strategies so that fungicide efficacy is maintained as long as possible. To that end, additional research is needed to understand the MOA, in cases where it is either unknown or not fully understood, to inform fungicide best-use practices and resistance management strategies.

Areas where additional research is needed are numerous. Much progress has been made but more is needed in understanding and characterizing the molecular mechanisms of the priming and elicitation of grapevine immunity. Research into breeding resistant cultivars utilizing QTLs should continue to support the introduction of new resistant cultivars to market in a relatively timely manner. As strongly resistant cultivars are developed, programs to encourage growers to plant these new cultivars will need to be employed. Additionally, exploration of the post-harvest or pre-bud burst application of microsporangia germination disruptors, such as *A. persicinum* or its metabolites, may lead to reduced inoculum for the next growing season. Continued research into effectors and how to suppress their function, by AMF or other means, may also lead to new treatment options. The development of methods to make plant extracts and essential oils more durable and rainfast is necessary to further their development as alternatives to chemical fungicides. While many challenges exist to exploiting hypovirulence to reduce the harmful effects of *P. viticola*, the discovery of hundreds of RNA viruses present in infected grape leaves opens the possibility of some of them being effective as mycoviruses.

Continually updating integrated disease management strategies based on the most current research knowledge and management options is essential. Strategies that can reduce the application of copper or other chemical fungicides are urgently needed; employing copper-reducing methods such as the microencapsulation of copper or using biomimetic synthetic hydroxyapatite could greatly reduce the amount of copper put into vineyards. Increased knowledge and continued trials of natural substances such as silica nanoparticles, BABA, DKPs, laminarin, and others, have the potential to reduce the rates of chemical fungicide application when applied in combination or alternation with other fungicides.

Many promising BCAs and natural substances have been identified and tested under various conditions. However, there are numerous hurdles to bringing them to market, including cost, having durable formulations, efficacy under various field conditions, and the stability of the product during storage, among others. While BCAs have not proven consistently effective under high-disease-pressure conditions, determining how to include BCAs and natural substances into integrated disease management plans either in mixtures or in alternation with other fungicides would help reduce the harmful effects of chemical fungicides and copper applications. Continued research into combining reduced rates of copper or other fungicides with *L. capsica* AZ78, laminarin, other BCAs, or their metabolites is necessary, and identifying combinations that support increased efficacy under field conditions could slow the development of fungicide resistance. However, care should be taken to determine if BCAs could pose any harmful effects to non-target species or ecosystems. Determining where BCAs fit into an integrated disease management program is greatly needed.

No management approach will eliminate the threat of downy mildew to grape cultivation. However, a better understanding of the pathogen, its genetics, and integrated disease management programs that optimize all available treatment options will help reduce its negative impacts to growers.

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