Threat of *Xylella fastidiosa* and options for mitigation in infected plants

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Abstract

The bacterial pathogen *Xylella fastidiosa* continues to threaten agricultural production of many different crops around the world, with significant economic burden from crop loss, disease management, and surveillance costs. In addition to direct economic consequences, plant diseases caused by *X. fastidiosa* have had significant societal impacts in the most affected regions. Although *X. fastidiosa* infects long-term perennial crops and landscape plants, there has never been a truly effective treatment for plants once they become infected. This review discusses the threat of *X. fastidiosa* to agriculture, landscapes, and global commerce, in addition to the most recent progress in treatment for *X. fastidiosa* in infected plants. Current disease mitigation options include nutritional, chemical, biocontrol, and plant resistance-based strategies, with the potential to develop combined management approaches. Overall, several strategies are promising for disease suppression but there is still opportunity for innovation, especially in treatment approaches that can be administered systemically by soil or foliar spray routes. Prevention of severe disease outcomes and crop loss, and the ability to suppress pathogen populations and reduce transmission without heavy reliance on insecticides would have significant economic and environmental benefits.

Keywords: *Xylella fastidiosa*, Pierce’s disease, citrus variegated chlorosis, almond leaf scorch, bacterial leaf scorch, olive quick decline syndrome

Review Methodology: This article discusses the recent developments in plant-focused strategies for *X. fastidiosa* management across its wide range of crop and ornamental host species. As the primary focus is on late-stage research for in planta control of the pathogen, innovations still in preliminary stages such as those tested in *vitro* or in model systems are not included. Literature reviewed for this article was obtained from searches of the Scopus and Web of Science databases using the following search terms: "*Xylella fastidiosa*, "Pierce’s disease," "citrus variegated chlorosis," "almond leaf scorch," "bacterial leaf scorch," "olive quick decline syndrome." From Scopus, this search returned approximately 1500 articles and from Web of Science approximately 2000 articles as of January 14, 2022. Additional research updates were included as appropriate from the publicly available proceedings of recent scientific meetings focused on *X. fastidiosa* in the United States (California Department of Food and Agriculture, Pierce’s Disease Research Symposium, December 14–15, 2021, https://www.cdfa.ca.gov/pdcp/) and Europe (3rd European Conference on *X. fastidiosa*, April 29–30, 2021, https://www.efsa.europa.eu/en/events/event/3rd-european-conference-xylella-fastidiosa-and-xf-actors-final-meeting). Articles were then curated manually for topic relevance, and with a focus on most recent findings. Several previous reviews cover other areas of *X. fastidiosa* research and earlier findings in more depth [1–9].

Threat of *Xylella fastidiosa*

*Xylella fastidiosa* is a bacterial species in the Xanthomonadaceae family, one of two species (*X. fastidiosa* and *Xylella taiwanensis*) in the genus *Xylella* [10, 11]. Three subspecies of *X. fastidiosa* have been formally described in bacterial taxonomy (subsp. *fastidiosa*, subsp. *multiplex*, and subsp. *paucia*) and additional subspecies (subsp. *sandyi*, subsp. *morus*) have been proposed as well [12–14]. The interactions of different *X. fastidiosa* subspecies, and different sequence types within a subspecies, with its wide range of host plants are complex. Some of the major *X.
fastidiosa subspecies—host interactions currently known to be associated with disease are listed in Table 1. However, this information is constantly evolving as new X. fastidiosa strains are identified and as genomic information provides additional insights into the genetic relationships of this pathogen. It is also important to note that within a host plant species, cultivar characteristics can influence susceptibility to different strains of X. fastidiosa as well.

### Agricultural crops, landscape, and global commerce

Major diseases caused by X. fastidiosa affect several economically significant specialty crops including grapes, almond, citrus, olive, blueberry, coffee, and stone fruits (Table 1). Worldwide, losses in agricultural production caused by this pathogen have been severe. In the early 2000s, loss of citrus trees due to X. fastidiosa infection was estimated to cost the industry in Brazil over $120 million US dollars per year [34]. Control of X. fastidiosa in the California grape industry has also reached over $100 million per year, and projected costs in the Mediterranean region due to this pathogen could be in the billions of euros, with a significant portion of these costs passed on to consumers [35–37]. Significance of X. fastidiosa to agricultural production has driven substantial research investments from national and state governments, and from grower-funded research programs [38]. As a result, considerable advances in understanding X. fastidiosa epidemiology and disease biology have occurred (especially over the last 30 years), with citrus, grapevine, Prunus species, and olive as the most highly studied host plants [1, 3–5, 20, 25]. In addition to the major crop hosts, X. fastidiosa can cause infection with or without disease symptoms in hundreds of plant species [39]. In ornamentals and wild plants, X. fastidiosa is not as well studied but ornamental plant trade has been implicated in some X. fastidiosa introductions [40, 41]. Woody perennials and trees often used in landscaping including oleander (Nerium oleander), ornamental olive (Olea sp.), myrtle-leaf milkwort (Polygala myrtifolia), American elm (Ulmus americana), and sycamore (Platanus spp.) are known hosts of X. fastidiosa in North America and Europe [12, 27, 28, 42, 43]. X. fastidiosa was also detected in ornamental coffee plants from Central America being imported into Europe [41]. The economic costs of managing and replacing diseased ornamental plants, and the impact on nursery trade are significant. In the southwestern United States, oleander is one of the most commonly used landscape plants in urban settings, including hedges along thousands of miles of roads and highways. Costs to cities and transportation authorities for plant removal and replacement are estimated in the millions of dollars [44, 45]. In the eastern United States, bacterial leaf scorch impacts a wide range of urban shade trees including in major cities such as Washington DC [46]. Because of the large size and value of trees in these settings, cost of replacing one tree can be thousands of dollars [47]. In areas where X. fastidiosa is not already established, eradication measures may be used if the pathogen is detected [48].

Propagation and transport of the infected plant material is an important risk factor for spread of X. fastidiosa both locally and globally [48]. Accordingly, detection and surveillance for X. fastidiosa in plant material is essential for reducing spread, but this comes with several challenges because of a long latent period (1–10 months, depending on host), and an extremely broad host range [39, 48]. Molecular detection protocols are typically the method of choice for X. fastidiosa in quarantine testing due to the difficulty and time required for culture-based methods. It is also important to identify the pathogen down to the level of subspecies or sequence type (based on multi-locus sequence typing) because not all sequence types of X. fastidiosa are virulent in all hosts, or restricted in the same areas [39, 49]. Improvements to molecular detection protocols for X. fastidiosa continue to be made with advances in molecular biology and sequencing technology [50–53]. However, as X. fastidiosa colonizes only the xylem tissue, sampling different plant organs and using different

<table>
<thead>
<tr>
<th>Host species</th>
<th>Disease common name</th>
<th>X. fastidiosa subspecies</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitis vinifera</td>
<td>Pierce’s disease (PD)</td>
<td>fastidiosa</td>
<td>[4, 11, 15]</td>
</tr>
<tr>
<td>Prunus dulcis</td>
<td>Almond leaf scorch</td>
<td>fastidiosa, multiplex</td>
<td>[16, 17]</td>
</tr>
<tr>
<td>Olea europaea</td>
<td>Olive quick decline syndrome (OQDS)</td>
<td>pauca</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>Citrus sinensis</td>
<td>Citrus variegated chlorosis</td>
<td>pauca</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>Vaccinium corymbosum</td>
<td>Bacterial leaf scorch of blueberry</td>
<td>fastidiosa, multiplex</td>
<td>[22, 23]</td>
</tr>
<tr>
<td>Prunus persica</td>
<td>Phony peach disease</td>
<td>multiplex</td>
<td>[1, 24]</td>
</tr>
<tr>
<td>Prunus domestica</td>
<td>Plum leaf scald</td>
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<td>[25, 26]</td>
</tr>
<tr>
<td>Nerium oleander</td>
<td>Oleander leaf scorch</td>
<td>sandyi</td>
<td>[12]</td>
</tr>
<tr>
<td>Polygala myrtifolia</td>
<td>Bacterial leaf scorch</td>
<td>multiplex</td>
<td>[27]</td>
</tr>
<tr>
<td>Platanus occidentalis</td>
<td>Bacterial leaf scorch</td>
<td>multiplex</td>
<td>[28]</td>
</tr>
<tr>
<td>Quercus sp.</td>
<td>Bacterial leaf scorch</td>
<td>multiplex</td>
<td>[29]</td>
</tr>
<tr>
<td>Coffea sp.</td>
<td>Coffee leaf scorch</td>
<td>pauca, fastidiosa/sandyi</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>Morus alba</td>
<td>Mulberry leaf scorch</td>
<td>morus</td>
<td>[32]</td>
</tr>
<tr>
<td>Chitalpa tashkentensis</td>
<td>Bacterial leaf scorch</td>
<td>taske</td>
<td>[33]</td>
</tr>
</tbody>
</table>

1This list is not exhaustive but contains the host plants for which significant findings have been published regarding X. fastidiosa infection and/or quarantine risk.
extraction procedures may be necessary for optimal detection depending on the plant species [54]. For field scale surveillance in areas where X. fastidiosa is already established, remote sensing technology is being explored in some crops, such as olive and almond, to facilitate the testing efforts in combination with other methods [55, 56]. Plant functional traits associated with water stress and chlorophyll degradation detected by aerial remote sensing of olive trees could distinguish symptomatic from asymptomatic trees prior to visual observation of symptoms on the ground [55]. In almond as well, plant spectral traits provided insight into disease spread when combined with epidemiological models [56]. Of particular interest is the potential for these technologies to differentiate symptoms of X. fastidiosa infection from abiotic water stress and other xylem pathogens such as Verticillium [57].

Spread of X. fastidiosa between host plants is dependent on insect transmission [2, 58], so field management also relies on identification and management of vectors. Understanding vector dynamics in the specific crop and geographic region is crucial as these dynamics can be vastly different depending on the area [59, 60]. In olive groves in the Apulia region of Italy where the spittlebug Philaenus spumarius is the predominant vector, the highest vector populations occur in late spring through early summer, with resurgence in the herbaceous groundcover plants again in autumn [61]. In contrast, populations of glassy-winged sharpshooter (GWSS), the main vector of X. fastidiosa in vineyards in the southern San Joaquin Valley region of California USA, peak in late summer [60]. Several other species of xylem-feeding insects have been implicated in other epidemics, also with different seasonal and spatial patterns of vector populations [62, 63]. As high vector populations are directly connected to the rate of pathogen spread, it is important to understand the region-specific dynamics in order to design the optimal management and risk mitigation strategies [64]. Besides insect vector dynamics, climate also impacts likelihood of X. fastidiosa establishment, with colder winters believed to limit disease persistence [65]. Additional climate variables such as precipitation and seasonal high temperatures are also important considerations [66]. Overall, the threat of X. fastidiosa to global agriculture production is significant and will continue to evolve as the environment in which we produce crops changes.

Societal impacts

Many plant pathogens throughout history have had far-reaching impacts on societies around the world and X. fastidiosa is no different. Diseases caused by X. fastidiosa have altered land use and crop selection, policy, social movements, and ecosystems. In the 1880s in the region of California, USA, now known as Orange County, Pierce’s disease had a significant impact on the viability of growing grapes and viticulture was largely abandoned in the area for the pursuit of other industries [9]. Likewise, in the eastern United States, Pierce’s disease pressure has been a limiting factor for the expansion of Vitis vinifera cultivation [67]. Crop substitutions and altered patterns of land use in response to pathogen pressure are a common consequence of plant disease, but the impact can be much greater in areas where the agriculture is directly tied to cultural identity.

The unforeseen epidemic of OQDS in southern Italy has had dramatic impacts not only on agricultural production, but also on cultural heritage and social dynamics. Olive trees in Apulia are often centuries old and hold great significance to the farmers and citizens of the region. Devastation brought on by the disease was not just in economic loss to the crops, but also in the less easily quantifiable value of some of the oldest olive trees in the Mediterranean basin, trees considered by many to be irreplaceable [68, 69]. Because of the cultural significance of the Apulian olive trees, X. fastidiosa eradication measures implemented by European authorities were met with resistance and social movements were formed in opposition [68–70]. Scientific uncertainty in the early stages of the OQDS outbreak in Italy was at times exploited to propagate misinformation about the pathogen, where it came from, and whether the containment policies were justified. This went as far as prosecution of several scientists who were actively working to find answers and solutions to the epidemic [71, 72]. As OQDS was first observed in olive trees in Italy around 2010, and X. fastidiosa was first detected in trees in the region in 2013, it demonstrates the unfolding of a major plant disease epidemic in the age of social media and rapid online communication [18, 69, 73]. It also highlights the importance of communicating effectively with agricultural stakeholders and the general public, and fully understanding the social context for emerging plant diseases just as for human diseases.

Social impacts of X. fastidiosa are not limited to rural agricultural regions. Trees and landscape plants in urban areas that provide significant health and environmental benefits are also threatened by this pathogen. Bacterial leaf scorch affects many of the shade tree species commonly planted in and around major eastern cities in the United States [29]. These trees provide important benefits to communities including atmospheric cooling, esthetic benefits, and mitigation of poor environmental conditions in urban areas [74]. Trees affected by X. fastidiosa can be found in parks, residential neighborhoods, and monuments such as the National Mall in Washington, DC. In some regions, it is estimated that up to 30% of urban landscape trees may be infected with X. fastidiosa [29]. However, in the United States the visible impacts on landscape outside of agriculture have not been as sudden or dramatic as what unfolded in Italy, and tree mortality from invasive diseases such as Dutch elm disease is typically more noticeable [29]. Like the olive trees of Apulia, ancient trees hold historical significance in other areas as well, such as the iconic oaks (Quercus robur) in England [75]. Although

http://www.cabi.org/cabireviews
X. fastidiosa has never been found in the United Kingdom, proactive research campaigns are ongoing to identify the potential native vectors and raise public awareness of the threat to English oak and other important plants should this pathogen arrive [76]. Preemptive risk mitigation efforts are not unwarranted given the dramatic impacts X. fastidiosa has had elsewhere in Europe over the last several years. Removal of olive groves leaving behind uncultivated land in the Apulia region of Italy led to loss of ecosystem services, particularly microclimate temperature regulation and habitat [68, 77]. Landscape restoration in peri-urban areas now requires consideration just as does the return of agriculture through re-planting either of X. fastidiosa-resistant olive varieties or of other crops.

**Options for Control.**

*Host resistance as a foundation for disease management.*

Historically, plant-focused management strategies for diseases caused by X. fastidiosa revolved around identification of existing resistant or tolerant plant material and/or development of new commercially desirable cultivars with improved X. fastidiosa resistance. Considerable work in breeding Pierce’s disease resistant grapevines in the United States utilized genetic material from American wild Vitis species naturally resistant to X. fastidiosa infection [78, 79]. This work identified a resistance locus (PDR1) that has since been used extensively in breeding Pierce’s disease-resistant wine grapes in the California region [80–83]. Likewise, in other crops such as citrus, olive, almond, and plum, screening of germplasm material or hybrid crosses revealed genetic material highly resistant to X. fastidiosa infection, or with some level of tolerance. Although the most common commercial Citrus sinensis varieties are susceptible, many hybrids and other citrus varieties including some mandarins (C. reticulata), lemons (C. lemon), and grapefruits (C. paradisi) have fewer symptoms, lower bacterial titers, or both [84]. Gene expression studies using resistant citrus varieties and hybrid crosses found induction of a number of plant defense genes associated with X. fastidiosa resistance [84–86]. In olive as well, certain cultivars such as “Leccino” have some resistance to X. fastidiosa, supporting lower bacterial populations and showing differential expression of defense-related genes [87]. Ongoing research to identify genetic diversity and more potential sources of X. fastidiosa resistance is being conducted on a wide range of European olive germplasm [88–90].

Prunus crops present an interesting case in X. fastidiosa resistance because there are several different species in this genus that are susceptible to different strains of the pathogen (almond leaf scorch, phony peach, plum leaf scald, etc.). Early graft transmission studies found that X. fastidiosa could be transmitted from root segments with phony peach symptoms to healthy plum scions and vice versa [91]. In more recent work, peach (P. persica) and peach-almond hybrid (P. persica × P. dulcis) varieties used for almond rootstock in California demonstrated resistance to an almond leaf scorch strain of X. fastidiosa [92]. However, this resistance is likely strain specific as peach cultivar “Nemaguard,” which is resistant to almond leaf scorch strains of X. fastidiosa, can become infected with phony peach disease [91, 93]. Among commercial almond varieties grown in the United States and Spain, there is also a range of susceptibility to X. fastidiosa, some of which is dependent on the specific pathogen strain [94–96]. Plum germplasm screening in Brazil also identified a range of susceptibility to leaf scald disease, including some cultivars that appear to be completely resistant [97, 98]. Given the presence of resistant genotypes in other Prunus species, it is likely that varietal resistance to phony peach disease exists as well, but this has not been fully evaluated [1]. What becomes increasingly clear is that resistance, tolerance, or susceptibility to X. fastidiosa is dependent on the specific X. fastidiosa strain and plant species and cultivar involved. Beginning to understand these interactions has been greatly facilitated by advances in genetic and sequencing technology, but not all X. fastidiosa lineages and host species are equally represented in available genome sequences to date and this is an important area of research going forward.

In addition to the traditional breeding efforts, other approaches in the realm of plant resistance include transgenics and the use of resistant rootstocks. Several different transgenic strategies have been tested in grapevines and citrus [99–102]. These strategies target specific pathogenesis mechanisms such as bacterial quorum sensing and polygalacturonase activity and complement pathogen-focused research in unraveling the disease mechanisms employed by X. fastidiosa in susceptible host plants [4, 6]. Because of consumer preference and regulatory hurdles related to transgenic plants in agriculture, protection of unmodified scions through the use of transgenic rootstocks is also being explored [101]. Naturally resistant rootstocks can also reduce disease symptoms or persistence of X. fastidiosa in some host plants. Almond trees grafted on peach rootstock “Nemaguard” not only had reduced scorching symptoms but also higher rates of recovery from disease compared with trees grafted on susceptible almond rootstock “Nonpareil” [93]. In blueberry, bacterial leaf scorch symptoms were reduced in a susceptible cultivar grafted on Vaccinium arboreum rootstock compared with own-rooted plants [103]. Likewise, in citrus some rootstocks such as “Rangpur” lime are highly resistant to X. fastidiosa, and substitution of infected scions for clean ones delayed return of citrus variegated chlorosis symptoms in Brazilian orchards under high disease pressure [104, 105]. Although some variation in Pierce’s disease severity was found in susceptible grapevines on different rootstocks, many commonly used grape rootstock varieties are not completely resistant to X. fastidiosa infection and scions will still be infected [106, 107]. In crops where grafting is typical, choice
of resistant rootstock could mitigate some \textit{X. fastidiosa} disease impacts but is unlikely to prevent infection altogether.

**Biological control—harnessing endophytes and defense priming**

One of the major challenges of targeting \textit{X. fastidiosa} once infection is established in plants is the specific localization of the pathogen in xylem tissue. Consequently, endophytic microorganisms that already reside in this niche are ideal for use in targeting \textit{X. fastidiosa}. Studies have been conducted in grapevine, citrus, and olive to identify endophytic microbes that could be antagonistic to \textit{X. fastidiosa} or otherwise reduce disease by triggering plant immune responses [108–113]. Some of the earliest biocontrol organisms tested against \textit{X. fastidiosa} in grapevine were non-virulent \textit{X. fastidiosa} strains [114]. Several non-virulent or weakly virulent \textit{X. fastidiosa} isolates from other host species (sycamore and elderberry) were inoculated into grapevines grown in vineyards under natural disease pressure in Florida, USA. Grapevines inoculated with \textit{X. fastidiosa} strain EB92-1 originally isolated from elderberry were protected from severe Pierce's disease for several years [114]. The mechanism of protection was believed to be an induced resistance response in the plant. More recent research found that \textit{X. fastidiosa} does in fact induce an immune reaction in grapevine and that one of the elicitors of this response is the bacterial outer membrane component lipopolysaccharide (LPS) [115, 116]. “Priming” of the plant immune response by prior exposure to purified \textit{X. fastidiosa} LPS leads to reduced disease symptoms in grapevine including both the externally visible scorching symptoms and tyloso formation in the xylem vessels that is implicated in water obstruction in the plant [116]. While it is still unclear whether this type of defense induction occurs universally in other \textit{X. fastidiosa}-host plant interactions, host immune priming is a promising avenue for future research.

A similar approach has been explored using unrelated endophytic bacteria to trigger systemic protection from \textit{X. fastidiosa} infection. A grapevine endophyte, \textit{Paraburkholderia phytofirmans} PSJN, can reduce disease caused by \textit{X. fastidiosa} both when the plants are inoculated with the biocontrol at the same time as infection challenge, and when the biocontrol is used up to 4 weeks after \textit{X. fastidiosa} inoculation in grapevine [117]. Unlike the biocontrol strains of \textit{X. fastidiosa} that need to be inoculated by needle puncture, PSJN can also be effectively established in host plants using a foliar spray of the bacterium in combination with an organo-silicon surfactant. The limiting factor in effectiveness of PSJN appears to be the length of time the biocontrol bacterial population is maintained in the plant. Preliminary tests of PSJN in olive found that durability of colonization may be limited, suggesting this species may not be as effective in all hosts of \textit{X. fastidiosa} [118]. However, research is ongoing to identify other potential biocontrol agents specific to olive and other hosts.

In addition to biocontrol organisms that induce an immune response, substantial work has been done to identify organisms living in the endosphere that are directly antagonistic to \textit{X. fastidiosa} through the production of secondary metabolites or competitive exclusion [108, 110, 111, 119]. In grapevine and citrus, some bacterial species including \textit{Pseudomonas fluorescens} (grapevine) and \textit{Curtobacterium flaccumfaciens} (citrus) were identified as negatively correlated with \textit{X. fastidiosa} infection symptoms [108, 110]. \textit{C. flaccumfaciens} also reduces the symptoms of \textit{X. fastidiosa} in periwinkle when co-inoculated [120] and was found in the foregut of sharpshooter vectors suggesting it can be transported between plants in a similar manner to the pathogen [121]. A range of bacteria were also isolated from olive endosphere, but none were identified as directly antagonistic to \textit{X. fastidiosa} [111]. Continued work to identify endophytes that can reduce \textit{X. fastidiosa} populations in susceptible crop hosts is ongoing. Alternatively, isolated secondary metabolite compounds produced by bacterial and fungal antagonists are also being explored, but none of these have completed testing as standalone treatments in plants [112, 122, 123].

**Chemical control—antibiotics, metals, and novel treatments**

Due to the extremely large economic consequences of disease and the value of some host plants, a wide range of antibiotic molecules have been considered to disrupt \textit{X. fastidiosa} infection. As with other methods, chemical treatments must target the xylem to be effective against \textit{X. fastidiosa}. Early research in an urban landscape setting found that American elm (\textit{U. americana}) with bacterial leaf scorch symptoms from \textit{X. fastidiosa} could be treated with microinjection of oxytetracycline [124]. Antibiotic-treated trees had remission of bacterial leaf scorch symptoms; however, the infection was not completely eliminated and would return if treatment was stopped [124]. Similar results were found with oxytetracycline injection in landscape oak trees [125] and in almond [126]. As traditional antibiotic treatment by injection methods is expensive and labor intensive, and comes with environmental concerns, recent research has focused on identifying other materials that can suppress \textit{X. fastidiosa} or mitigate symptoms. Due to the disruption of metal homeostasis in plants infected with \textit{X. fastidiosa} and the common use of metals such as copper for control of bacterial pathogens in agriculture, several of the newer strategies include some form of copper or zinc [127]. Although not strictly bactericidal at concentrations that can be maintained in xylem fluid, copper and zinc can disrupt \textit{X. fastidiosa} disease-related phenotypes such as...
exopolysaccharide production and biofilm development [128, 129]. It is worth noting, however, that different \textit{X. fastidiosa} strains have varied tolerance to copper, and tolerance level can be further influenced by physiological state of the bacterial cells (biofilm vs. planktonic vs. persistent states) [130–133]. In olive trees in Italy, products containing copper, zinc, citric acid, and botanical extracts (Dentamet®, NuovOlivo) had some success at mitigation of OQDS symptoms in areas with high \textit{X. fastidiosa} incidence [134, 135]. Specific disease suppression mechanisms of these products are not completely understood, but success could be associated with plant-induced defenses, plant nutrition, or influence on \textit{X. fastidiosa} disease progression.

With technological improvements in chemical formulations, there is now possibility to deliver the bactericidal treatments to the vascular tissue more effectively \textit{via} uptake from soil or as foliar spray. Nano-formulations of zinc oxide, which are effective in suppression of other bacterial plant diseases (such as citrus canker caused by \textit{Xanthomonas citri}, [136]) have shown promising initial results against \textit{X. fastidiosa} in blueberry [137]. These compounds are able to be taken up systemically by plants and treatment of \textit{X. fastidiosa}-infected blueberry plants reduced bacterial populations and disease symptoms [137].

Due to the importance of biofilm development in \textit{X. fastidiosa} pathogenesis and transmission, many chemical control strategies also target the biofilm process [138]. One such compound, the cysteine analog N-Acetylcysteine (NAC), was tested in citrus and olive with some success in reducing symptom progression [139, 140]. In some citrus plants treated with NAC, symptom remission was observed as well [140]. However, high disease pressure under field conditions and highly susceptible host varieties reduced the effectiveness of NAC in olive [139]. Overall, although none of the products tested so far are able to cure the infection completely, there is some success with disease symptom mitigation, and additional antimicrobial products are still being explored [123, 138].

\textbf{Specific targeting with parasitic phages}

Several bacteriophages that infect \textit{X. fastidiosa} have been identified and tested for the management of Pierce’s disease of grapevine. Siphophages Sano and Salvo, and podophages Prado and Paz were originally isolated from plant material and are virulent on strains of \textit{X. fastidiosa}, in addition to some \textit{Xanthomonas} strains [141]. These four phages were tested for virulence on 50 \textit{X. fastidiosa} isolates, mostly strains isolated from grapevine, but also several other isolates from different hosts [142]. Used in combination as a phage cocktail delivered into grapevines \textit{via} trunk injection, Sano, Salvo, Prado, and Paz can reduce the symptoms of Pierce’s disease as well as bacterial populations within the plant. However, \textit{X. fastidiosa} was not completely eliminated from the infected grapevines in this study [142]. Although phage-resistant \textit{X. fastidiosa} mutants are able to develop \textit{in vitro}, in the case of Sano, Salvo, Prado, and Paz, phage-resistant \textit{X. fastidiosa} mutants were not virulent in planta likely due to the phage target (type IV pili) being important for plant colonization [142]. Several additional phages were identified more recently from insect vectors of \textit{X. fastidiosa} and from environmental samples. These phages from the \textit{Podoviridae} and \textit{Siphoviridae} families are virulent on strains of \textit{X. fastidiosa} found in the Mediterranean region [143]. Although these have not yet been tested for disease suppression in planta, it suggests that phages targeting \textit{X. fastidiosa} can be found in a number of different environments and there is promise for developing this technology further in the future.

\textbf{Conclusions}

Although there is still no cure, the range of treatments in development for \textit{X. fastidiosa}-infected plants is encouraging. In addition to direct applications, exploration of various treatment strategies also produced significant information about disease mechanisms to be used for more targeted future efforts. The substantial progress in \textit{X. fastidiosa} research is a direct result of significant financial investment from federal, state, and private entities [38]. Although much of the existing research is focused in the Americas and Europe, \textit{X. fastidiosa} also impacts other regions including the Middle East and parts of Asia [126, 144, 145]. It is important to consider solutions that can be adapted for specific regions, crops, local disease dynamics, and resource availability. There is continued need for research in plant-focused solutions as concern about insecticide resistance emerges in relation to reliance on vector control [146]. Although technological advances in genomics, molecular breeding, and germplasm screening will expedite generation of resistant plant material, this is still a lengthy task due to the wide range of perennial host plant species impacted by \textit{X. fastidiosa}. Hopefully in the future, integrated management will be possible through combining cultivation of resistant or tolerant plants with defense priming, nutritional support, and bactericidal treatments in addition to the existing phytosanitary and vector control measures (Fig. 1).

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