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REVIEW

A review of the use of phosphonates in the management of *Phytophthora nicotianae* in citrus in South Africa

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Abstract *Phytophthora* species are important pathogens of citrus. They cause fibrous root rot, among other diseases, that lead to significant yield losses of economic importance. The management of *Phytophthora* diseases of citrus relies on chemicals of which phosphonates form an integral part. Phosphonates are unique in their complex, multipronged mode of action that remains poorly understood. Due to this attribute, they are considered to be at low risk of resistance development. Despite this, there have been recent reports of reduced phosphonate sensitivity in various *Phytophthora* species including those of relevance to citrus. Therefore, resistance management strategies guided by evolutionary principles should be strictly adhered to, to avoid the selection of resistant strains and a concomitant population shift in sensitivity. Knowledge of fitness costs associated with reduced phosphonate sensitivity in *Phytophthora* is lacking. Therefore, the aim of this review was to compile the available information on phosphonates and their current efficacy against *Phytophthora* diseases of citrus in South Africa. Resistance management strategies guided by evolutionary principles and the relevance of fitness costs were also investigated.

Keywords Root rot · Phytophthora nicotianae · Phosphonates · Oomycetes

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Introduction

Citrus is an important agricultural commodity globally and in South Africa, accounting for a substantial market share of total agricultural production (DAFF, 2020). The South African citrus industry is an important player on the international stage. During the 2022 production season, approximately 3.2 million tons of fresh citrus were produced in the country of which more than 2.6 million tons were exported, making South Africa the 10th largest producer and second largest exporter of fresh citrus in the world (CGA, 2023). Citrus production accounted for R16.1

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billion of the total South African agricultural production market value as of the 2018/19 production season (DAFF, 2020). Nearly 100 thousand hectares of citrus are planted across South Africa, with Limpopo accounting for the largest share (39,524 ha), followed by the Eastern Cape (24,508 ha), Western Cape (19,208 ha), Mpumalanga (8127 ha), KwaZulu-Natal (2350 ha), Northern Cape (1818 ha), North West (730 ha), and the Free State (12 ha), in that order (CGA, 2023). The main varieties planted in the country are Valencia/Midseason, Mandarins, Lemons, Navels, and Grapefruit, in decreasing order of planted areas (CGA, 2023). Citrus trees are woody perennials with lifespans that can exceed a century, during which time they constantly face various biotic and abiotic challenges including from oomycetes such as *Phytophthora* (Dalio et al., 2017).

Phytophthora species are the most important soil- and water-borne pathogens of citrus and the causal agents of fibrous root rot (Graham & Feichtenberger, 2015). This disease can cause tree death and decline, resulting in poor yields and substantial revenue losses to the industry (Graham & Feichtenberger, 2015; Graham & Menge, 1999). The management of *Phytophthora* diseases in citrus depends heavily on the use of oomycide chemicals such as phosphonates (Dewdney & Johnson, 2022; Farih et al., 1981; Hao et al., 2020; Le Roux, 2003). Phosphonates have a complex mode of action that remains largely unknown, although it is proposed to involve a combination of direct pathogen inhibition and stimulation, or priming, of host plant defences, both directly and indirectly (Dann & McLeod, 2021; Fenn & Coffey, 1987; Guest & Grant, 1991). They are ambimobile and will accumulate in actively growing tissues in the plant (Dann & McLeod, 2021; Guest & Grant, 1991; Guest et al., 1995; Nartvaranant et al., 2004; Whiley et al., 1995).

Due to their complex mode of action, phosphonates are classified as low risk for resistance development (Fungicide Resistance Action Committee, 2022). Despite this, *Phytophthora* species with reduced phosphonate sensitivity have been reported (Belisle et al., 2019; Dobrowolski et al., 2008; Duvenhage, 1994; Fenn & Coffey, 1987; Veena et al., 2010; Wilkinson et al., 2001a), including *P. nicotianae* from citrus (Adaskaveg et al., 2017; Hao et al., 2020). Therefore, to ensure the continued efficacy of these products, resistance management strategies, such as mixing or alternating phosphonates with other oomycides with different mechanisms of action, should be strictly adhered to (Corkley et al., 2022).

Knowledge of the underlying evolutionary origins of pesticide resistance is important for risk assessment and resistance management (MacLean et al., 2010; Neve et al., 2014). Pesticide resistance can arise from de novo mutations that occur after its introduction, from standing variation already present in the population, or from the transfer of resistance from resistant species by hybridisation and horizontal gene transfer (Hawkins et al., 2019). Accordingly, the risk of resistance development depends on the level of standing variation, the de novo mutation rate, and the relative resistance and fitness conferred by each under pesticide selection (Hawkins et al., 2019).

When incorporating evolutionary principles into resistance management strategies, factors to consider include the number of pesticide applications (Hobbelen et al., 2014; Van den Bosch et al., 2014a; Van den Berg et al., 2016), the type of resistance (i.e., major- or polygenic resistance) and how this relates to the dosage rate (Roberts et al., 2008; Manalil et al., 2011; Van den Bosch et al., 2011; Van den Bosch et al., 2014a), whether applications are preventative or curative (Brent & Hollomon, 2007; Van den Bosch et al., 2014a; Cohen et al., 2018; Corkley et al., 2022), and whether pesticides with different mechanisms of action are mixed or alternated (Shaw, 2006; Brent & Hollomon, 2007; Van den Bosch et al., 2014a; Van den Bosch et al., 2014b; Corkley et al., 2022). Such strategies aim to minimise the difference in growth rates between resistant and sensitive strains to reduce selection of the former (Milgroom & Fry, 1988; Van den Bosch & Gilligan, 2008). Theoretically, resistance management strategies can completely prevent resistance development and simultaneously maintain successful disease control with the help of fitness penalties, among other factors (Corkley et al., 2022; Hawkins & Fraaije, 2018; Mikaberidze et al., 2014).

The development of pesticide resistance in a strain can come at the expense of its ability to survive, reproduce, and compete with other strains in the absence of pesticide exposure if the resistance mechanism disrupts physiological or biochemical functions. This is known as a fitness cost (Hawkins & Fraaije, 2018; Zhan & McDonald, 2013). Various mechanisms underlie fitness costs, including reduced activity or efficacy of mutated target sites and resource allocation costs from the over-expression of targets

or an up-regulation in active transport (Hawkins & Fraaije, 2018).

An evolutionary trade-off between the advantages of resistance versus its fitness cost can affect whether resistance becomes established in the population (Hawkins & Fraaije, 2018; Zhan & McDonald, 2013). Epistatic effects of the genetic background, such as compensatory mutations in other genes that offset the burden of the initial resistance mutation, can also play a role in the establishment of a resistance trait in the population (Corkley et al., 2022; Hawkins & Fraaije, 2018; Lalève et al., 2014). Under non-selective conditions, such as periods devoid of pesticide exposure, a fitness cost can prevent the establishment of resistance. Therefore, given adequate time between pesticide treatments, resistance evolution can be reversed (Hawkins & Fraaije, 2018). Conversely, resistant mutants that do not carry fitness costs will persist, rendering the pesticide permanently ineffective (Zhan & McDonald, 2013). It follows that fitness costs have implications for resistance management strategies and resistance risk assessments of pesticides (Hawkins & Fraaije, 2018; Hollomon, 2015; Hu et al., 2008).

Fitness costs vary under different environmental conditions, host genetics, pathogen life stages, and genetic backgrounds in which the mutation occurs (Hawkins & Fraaije, 2018; Kawecki & Ebert, 2004; Zhan & McDonald, 2013). Consequently, experiments have yielded inconsistent findings of fitness costs associated with fungicide resistance. Nowhere is this more apparent than with phenylamide resistance in *Phytophthora* species (Café-Filho & Ristaino, 2008; Chapara et al., 2011; Hu et al., 2008; Timmer et al., 1998). There is a knowledge gap concerning fitness costs associated with reduced phosphonate sensitivity in *Phytophthora* species. A single known study that investigated fitness costs associated with a phosphonate-resistant mutant strain of *Phytophthora capsici* found none (Lucas et al., 1990).

This review summarises the current literature on phosphonates as a treatment modality for *Phytophthora* diseases, with special emphasis placed on *Phytophthora nicotianae*, the most common species on citrus in South Africa. This review discusses the mode of action of these chemicals and their current efficacy. Recent reports of reduced phosphonate sensitivity in *Phytophthora* warranted a discussion of resistance management practices driven by evolutionary principles. Fitness costs associated with resistance and its relevance to resistance management are also discussed.

Phytophthora and related pathogens of citrus

Phytophthora species are the most important soil- and water-borne pathogens of citrus, causing diseases including damping-off of seedlings, foot and root rot of young trees in nurseries, and foot rot, fibrous (feeder) root rot, and brown rot in mature trees in orchards (Graham & Feichtenberger, 2015). *Phytophthora* foot and root rot are serious threats to citrus production worldwide (Timmer et al., 1998). Foot rot is associated with characteristic gum-like oozing from trunk lesions and is therefore also referred to as gummosis. Infection of a susceptible scion starts near the soil line and can spread up the trunk towards the graft union (Graham & Feichtenberger, 2015). The cambium and inner bark are affected, and lesions can spread to girdle the entire trunk, especially of younger trees with smaller diameter trunks, resulting in tree death. In older trees, the trunk is less frequently girdled, and the tree canopy displays symptoms of chlorosis, defoliation, dieback, and poor growth flushes (Erwin & Ribeiro, 1996; Graham & Feichtenberger, 2015). Fibrous root rot is characterised by terminal rot of the feeder roots, resulting in sloughing-off of the periderm and cortex to expose the underlying white stele (Erwin & Ribeiro, 1996; Thompson et al., 1995). On susceptible rootstocks, it can cause tree death, especially in young trees. Conversely, mature trees are rarely killed and normally show symptoms of decline such as chlorosis, defoliation, dieback, reduced fruit production (in terms of size and yield), and overall poor growth (Graham & Feichtenberger, 2015). Although yield losses from root rot are difficult to quantify, when left untreated, it is estimated at 3 – 6% of the total yield in Florida (Graham & Feichtenberger, 2015; Graham & Menge, 1999). Citrus fruit infection, which can become apparent pre- or post-harvest, is known as brown rot. It is characterised by light brown lesions with a leathery texture on the fruit rind (Graham & Feichtenberger, 2015; Graham & Menge, 2000; Hao et al., 2020).

Several *Phytophthora* species are known pathogens of citrus, although *P. nicotianae* Breda de Haan (syn. *Phytophthora parasitica* Dastur) and *P. citrophthora* (R.E. Sm. & E.H. Sm.) Leonian are considered

the most important worldwide (Graham & Feichtenberger, 2015). In South Africa, *P. nicotianae* is the predominant species, with a country-wide distribution, while *P. citrophthora* is mainly restricted to the cooler production regions like the Western- and Eastern Cape, although it has been isolated elsewhere (Maseko & Coutinho, 2002; Meitz-Hopkins et al., 2014; Thompson et al., 1995). *Phytophthora nicotianae* is found most often in warmer regions, as it grows in a temperature range of 8 to 36 °C, with an optimum growth temperature of 31 °C. *Phytophthora citrophthora* has an optimum temperature of 26 °C, growth range of 6 to 32 °C (Dirac et al., 2003; Matheron & Porchas, 1996), and is thus more prevalent in cooler climates. Accordingly, the warmer provinces of South Africa tend to favour *P. nicotianae*, while cooler climates are more favourable to *P. citrophthora* (Meitz-Hopkins et al., 2014). There might also be a seasonal influence on the prevalence of these species, with *P. nicotianae* being more prevalent during the warmer months and *P. citrophthora* during the cooler ones (Alvarez & Gramaje, 2009; Dirac et al., 2003; Timmer et al., 1989). Other *Phytophthora* species implicated in disease are *P. palmivora* (Butler) and *P. hibernalis* Carne, both of which cause brown rot, while the former can also cause root rot under adverse conditions (Graham & Feichtenberger, 2015). These species can occur in coinfections, resulting in more severe disease (Panabières et al., 2016). In warm climates like that of Florida, *P. nicotianae* may co-occur with *P. palmivora* (Graham et al., 1998), whereas under Mediterranean climates, *P. nicotianae* often co-occurs with *P. citrophthora* (Alvarez et al., 2011; Cohen et al., 2003).

Coinfections beween *Phytophthora* spp. and other genera can occur. The association between the diaprepes root weevil (DRW), *Diaprepes abbreviates* and *Phytophthora* species, known as the PD-complex, promotes root rot caused by the latter. Larval feeding by the DRW predisposes fibrous roots to more severe infection by *Phytophthora*, especially on susceptible rootstocks such as sour orange and Cleopatra mandarin (Graham & Feichtenberger, 2015; Graham et al., 2003). Control strategies for this association must integrate the control of both *Phytophthora* and *Diaprepes* (Graham et al., 2003). Huanglongbing (HLB) syndrome, also called citrus greening (Bové, 2006), is a vascular disease that results in reduced fruit size and quality, and eventually leads to tree death (Graham et al., 2013). It is caused by one of three fastidious Gram-negative bacteria of the genus *Candidatus* Liberibacter namely, *Candidatus* Liberibacter africanus (CaLaf), *Ca*. L. asiaticus (CaLas), and *Ca*. L. americanus (CaLam). It is transmitted by psyllid vectors, but also by grafting (Gottwald, 2010). It infects all plant parts including roots, predisposing them to infection by root pathogens like *P. nicotianae* (Panabières et al., 2016). This predisposition appears to result from the increased attraction of zoospores to roots and the breakdown of root defence mechanisms (Graham et al., 2011). The association between the HLB agent and *Phytophthora*, known as the HLB-*Phytophthora* complex, leads to greater root damage than caused by either pathogen alone (Graham & Feichtenberger, 2015; Graham et al., 2013). Management of this complex requires an integrated approach that targets both pathogens (Panabières et al., 2016). The efficacy of phosphonate fungicides, which activate host defences against *Phytophthora*, might be ineffective in roots already damaged by HLB (Graham et al., 2011). Therefore, a chemical with a direct mode of action, like mefenoxam, is necessary in such cases (Panabières et al., 2016). Conversely, other parasites or pathogens can have an antagonistic effect on *P. nicotianae* in coinfections of citrus. Roots infected by the citrus nematode *Tylenchulus semipenetrans,* were significantly less susceptible to infection by *P. nicotianae* compared to roots uninfected by the former. Furthermore, root rot severity was significantly reduced in coinfected citrus roots compared to roots solely infected by the oomycete (El-Borai et al., 2002). Similarly, evidence suggests that mildly pathogenic strains of *Fusarium solani*, the causal agent of dry root rot in citrus, have a suppressive effect on *P. nicotianae* in coinfections of citrus. This effect is only observed when inoculation with *F. solani* occurs prior to or simultaneously with *P. nicotianae*. Therefore, non-pathogenic strains of *F. solani* might offer protection against Phytophthora root rot (Dandurand & Menge, 1992; Strauss & Labuschagne, 1994).

There are many potential sources of *Phytophthora* inoculum. In citrus nurseries in Florida and São Paolo, the main sources of *P. nicotianae* were found to be contaminated surface water, such as irrigation water, and run-off from nearby groves. Rootstock seedlings were also a common source of the pathogen in these nurseries (Graham & Feichtenberger, 2015). In Oregon horticultural nurseries, the main sources of

Phytophthora inoculum were latently infected plants, potting media, containers, and soil/gravel from walkways in the greenhouse, container yards, and the surrounding fields. Materials used in early propagation from cuttings and tissue culture were a lesser source of inoculum. Irrigation water, not treated with sodium hypochlorite, contained a diverse collection of species although very few were known plant pathogens (Parke et al., 2014). Chlamydospores and oospores of *P. nicotianae* are known to survive in soil and plant material for many years (Erwin & Ribeiro, 1996; Gallup et al., 2006; Hemmes, 1983; Weste, 1983). Both these spores can survive the gastrointestinal tract and faeces of various animals including, birds, snails, and termites, facilitating their dispersal (Alvarez et al., 2009; Weste, 1983). Chlamydospores can also be dispersed by irrigation and rainwater, as well as through the movement of contaminated soil (Panabières et al., 2016; Thomson & Allen, 1976). *Phytophthora citrophthora* does not survive as long as *P. nicotianae.* Linderman and Davis (2006) failed to recover *P. citrophthora* from soil inoculated with oospores and chlamydospores two months after inoculation. Gerlach et al. (1975), however, found that mycelium of the pathogen survived for approximately 40 weeks in infected leaves in contact with soil, depending on the moisture content of the soil.

Phytophthora nicotianae

The genus *Phytophthora* is composed of at least 212 described species along with many more provisional species, arranged into 16 phylogenetic clades, with *P. nicotianae* falling in Clade 1 (Abad et al., 2023). Of all the *Phytophthora* species, *P. nicotianae* is one of the most important in terms of its distribution, host range, and agronomic impact. It can cause severe losses on a large range of host plants (Panabières et al., 2016). It was first described in 1896 on tobacco (Erwin & Ribeiro, 1996). Since then, it has been reported on 255 plant genera from 90 families (Cline et al., 2008), including those with other *Phytophthora* species as their primary pathogens such as avocado, normally infected by *P. cinnamomi* Rands (Machado et al., 2013), apples, normally infected by *P. cactorum* (Lebert & Cohn) J. Schröt. (Erwin & Ribeiro, 1996; Souli et al., 2014), and chilli peppers, normally infected by *P. capsici* Leonian (Allagui & Lepoivre, 2000).

Like many other *Phytophthora* species, *P. nicotianae* is hemibiotrophic. At the beginning of infection, it suppresses host plant basal defences and exists biotrophically, whereafter it switches to a necrotrophic lifestyle (Panabières et al., 2016). The *P. nicotianae* lifecycle consists of both asexual and sexual phases (Meitz-Hopkins et al., 2014; Panabières et al., 2016). Specialised hyphal structures called sporangiophores produce asexual, multinucleate sporangia that may germinate directly or release uninucleate zoospores, depending on water availability and temperature (Erwin & Ribeiro, 1996; Panabières et al., 2016). Zoospores contain two flagella each, enabling them to move toward host plants by chemotaxis and electrotaxis, among other mechanisms (Walker & van West, 2007). Host recognition causes zoospore encystment and germination, generating a germ tube that penetrates the plant (Ludowici et al., 2013). Due to it being heterothallic, *P. nicotianae* can sexually reproduce only in the presence of the opposite (A1 or A2) mating type (Meitz-Hopkins et al., 2014; Panabières et al., 2016). This attribute contributes to increased genetic diversity, potentially facilitating adaptation to changing environmental pressures (Meitz-Hopkins et al., 2014). The fusion of male and female gametangia produces sexual survival structures called oospores that can persist in soil for years (Hemmes, 1983; Panabières et al., 2016; Weste, 1983). Upon germination, oospores either produce sporangia that can release zoospores, or directly form germ tubes that can infect the host (Erwin & Ribeiro, 1996). Under adverse conditions, such as unfavourable temperatures and humidity, *P. nicotianae* can produce asexual survival structures, called chlamydospores, that can survive for up to six years outside a host in soil and plant tissues (Erwin & Ribeiro, 1996; Gallup et al., 2006).

On a transient basis, *P. nicotianae* might be a secondary pathogen to other *Phytophthora* species with more limited host ranges, such as *P. citrophthora* and *P. palmivora* in citrus (Erwin & Ribeiro, 1996; Panabières et al., 2016). However, it possesses certain attributes that make it a superior competitor to other species in the genus. As previously noted, it has higher cardinal temperatures than most of its competitors (Erwin & Ribeiro, 1996), allowing it to dominate under warmer conditions (Panabières et al.,

2016). Furthermore, its dispersal in irrigation water is possibly superior to that of its competitors as its zoospores are liberated after only brief exposure to water, and remain motile for up to 20 h, allowing it to reach its host faster than its competitors (Thomson & Allen, 1976). The rapid release of zoospores following brief contact with water also enhances dispersion by splashing from rain and irrigation (Panabières et al., 2016). Besides chlamydospores that can survive for long periods outside a host (Erwin & Ribeiro, 1996; Gallup et al., 2006), *P. nicotianae* also produces other structures such as cysts, hyphal fragments, microsporangia, and appressorium-like structures that are known to remain viable in irrigation water for up to 60 days (Thomson & Allen, 1976). These attributes of *P. nicotianae* might help explain its increasing prevalence in new hosts and geographic locations.

Notwithstanding its wide host range, evidence in the form of pathogenicity tests and mitochondrial- and nuclear single nucleotide polymorphisms (SNPs), suggests host specialisation within the *P. nicotianae* population (Biasi et al., 2016; Kamoun et al., 2015; Panabières et al., 2016; Taylor et al., 2012). This was especially apparent in citrus isolates from across the globe that clustered together in a single mitochondrial group and shared one or more nuclear alleles (Mammella et al., 2011, 2013), a discovery that was partly supported by microsatellite marker data (Biasi et al., 2016). In contrast, isolates collected from nurseries were more heterozygous and balanced in terms of the prevalence of the A1 and A2 mating types (Biasi et al., 2016). The predominance of the A1 mating type in citrus groves from various surveys, including in South Africa, supports the hypothesis of clonal reproduction in these locations (Biasi et al., 2016; Mammella et al., 2013; Meitz-Hopkins et al., 2014). A lack of geographic genetic structuring within most of the *P. nicotianae* population, in addition to the observed host specialisation (Biasi et al., 2016; Mammella et al., 2013), suggests considerable migration via infected plant material followed by the progressive divergence of lineages by host specialisation (Panabières et al., 2016). The westernisation of diets across the globe has led to increased trade in temperate fruits and vegetables (Pingali, 2007), many being potential hosts of *P. nicotianae*. This has promoted the spread of this pathogen, increasing its significance worldwide (Panabières et al., 2016).

Management of *Phytophthora nicotianae* diseases of citrus

The management of *Phytophthora* diseases of citrus requires an integrated approach that includes the use of resistant/tolerant rootstocks, cultural practices, and chemical treatments. Resistant rootstocks can become infected without rotting, whereas tolerant ones generate new roots to offset root mass losses from disease (Graham, 1995; Kosola et al., 1995). Most rootstocks have some level of resistance to foot rot but resistance/tolerance to root rot varies, depending on the cultivar and *Phytophthora* species (Graham & Feichtenberger, 2015). Carrizo citrange (*Citrus sinensis* (L.) x *Poncirus trifoliata* (L.) Raf.) and Rough Lemon (*Citrus jambhiri* Lush.) are two commonly used rootstocks in South Africa (Meitz-Hopkins et al., 2014). The former is tolerant, while the latter is susceptible to *P. nicotianae*-induced root rot (Graham & Feichtenberger, 2015; Le Roux, 2003; Timmer et al., 1998). Rough Lemon has various properties that make it a popular rootstock choice despite being highly susceptible to *Phytophthora*. Trees on these rootstocks are tolerant to *Citrus tristeza virus* (CTV) and citrus viroids (CVd), and tolerate high pH and coarse, sandy soils. Also, due to their high vigour, trees on these rootstocks have large fruit sizes and yield and recover rapidly from cold damage. It is highly compatible with Eureka lemon (*Citrus limon* (L.) Burm f.) and therefore remains the rootstock of choice (CRI, 2016).

The mechanisms underlying rootstock resistance to *Phytophthora* are largely unknown. However, genes and quantitative trait loci (QTL) conferring resistance have been identified from the resistant rootstock *Poncirus trifoliata* (Chen et al., 2008; Siviero et al., 2006), suggesting the importance of quantitative traits in rootstock resistance (Boava et al., 2011). Differences in rootstock resistance might arise from different levels of expression of pathogenesis-related (PR) protein genes as well as those involved in the hypersensitive response (HR), cell wall modifications, and the production of phytoalexins and reactive oxygen species (ROS) (Albrecht & Bowman, 2008; Boava et al., 2011). Host resistance can also arise from the inability of *P. nicotianae* to overcome preformed physical and biochemical barriers to infection, or the absence of pathogen effector targets in the

host (Dalio et al., 2018). Defence against biotrophs is usually modulated by salicylic acid (SA)-dependent signalling (Boava et al., 2011), leading to the synthesis of PR proteins, the accumulation of ROS, and localised necrosis (Park et al., 2009). In contrast, defence against necrotrophs is usually controlled by jasmonic acid (JA)- and ethylene (ET)-dependent signalling that induces alternative PR proteins (Cordelier et al., 2003). These two contrasting signalling pathways interact synergistically and antagonistically (De Vos et al., 2005). In the case of a hemibiotroph like *P. nicotianae*, where the infection starts with a biotrophic phase followed by a necrotrophic phase, both these pathways are likely to be active at different stages of infection (Attard et al., 2010; Boava et al., 2011).

High soil moisture conditions, such as during waterlogging, promote *Phytophthora* infection (Feld et al., 1990). Under saturated soil conditions, fibrous roots can become infected within hours, decay, and die within four to six weeks (Graham & Feichtenberger, 2015). Therefore, planting in well-drained soils and avoiding over-watering are essential practices (Graham & Feichtenberger, 2015; Joubert & Labuschagne, 1998). Poor soil drainage can also be managed with drainage tiles and ditches (Graham & Feichtenberger, 2015). Soils high in calcium bicarbonate and pH should also be avoided as these conditions are unfavourable for rootstocks (Graham & Feichtenberger, 2015). Water is a potential source of infective *Phytophthora* propagules, and it is therefore important to use clean irrigation water and avoid runoff from the surrounding areas (Graham & Feichtenberger, 2015; Kong et al., 2003; Van Niekerk et al., 2019). Chlorination with at least 6 ppm active chlorine for at least 60 min is necessary for the elimination of all *Phytophthora* propagules (Van Niekerk et al., 2019).

The production of disease-free nursery plants is another important component of disease management (Graham & Feichtenberger, 2015). *Phytophthora nicotianae* is a prevalent species found in nurseries that cultivate potted ornamental and fruit tree varieties, with trade practices likely facilitating the spread of this pathogen (Baysal-Gurel et al., 2021; Weiland, 2021). The environmental conditions typical of commercial nurseries, such as elevated temperatures, consistent irrigation, inadequate drainage, and high seedling density, are conducive to the emergence of localized disease outbreaks caused by *Phytophthora* species (Simamora et al., 2016). Regular testing and treatment of rootstocks using phosphonate and mefenoxam, along with effective agricultural practices such as managing irrigation, chlorinating irrigation water, removing infected seedlings, keeping trees elevated on plinths or platforms, and ensuring proper runoff of irrigation water, are strategies utilized in many citrus nurseries.

The susceptibility of roots to infection by *Phytophthora* species shows seasonal variability (Dirac et al., 2003; Matheron et al., 1997). Therefore, oomycide applications should coincide with periods of high root susceptibility which occur during root flushes following leaf flushes in spring and autumn (Dewdney & Johnson, 2022; Graham & Feichtenberger, 2015). Phosphonates, phenylamides, and copper compounds have traditionally been used for the control of *Phytophthora* diseases of citrus (Dewdney & Johnson, 2022; Farih et al., 1981; Hao et al., 2020; Le Roux, 2003). More recently, two new oomycota fungicides namely fluopicolide and mandipropamid have successfully been used abroad (Belisle et al., 2022; Dewdney & Johnson, 2022; Hao et al., 2020). In the case of resistant/tolerant rootstocks, fungicide treatment should be for at least one growing season, whereas for susceptible rootstocks, it should continue for longer (Graham & Feichtenberger, 2015).

Phosphonates for the management of *Phytophthora nicotianae*

Phosphonates are the preferred chemicals for the management of *Phytophthora* diseases due to their relatively low cost, preventative and curative action, and resistance development to the phenylamides (Hao et al., 2020; Van Niekerk et al., 2019). The term “phosphonate”, in the context of anti-oomycete or oomycide crop protection products, refers to the salts and esters of phosphonic acid (H_3PO_3) (Dann & McLeod, 2021; Guest & Grant, 1991). Confusingly, the term also denotes compounds with phosphorus-hydrogen or phosphorus-carbon bonds, such as the synthetic organophosphorus insecticides and the herbicide, glyphosate, which are quite different from the salts and esters of phosphonic acid (Guest & Grant, 1991; Guest et al., 1995; McDonald et al., 2001). Further confusion arises due to the interchangeable use

of the terms, phosphorous acid and phosphonic acid. According to the rules of the International Union of Pure and Applied Chemistry (IUPAC), phosphorous acid refers to the anhydrous solid ($(OH)_3P$), that only changes to phosphonic acid once dissolved in water (Guest & Grant, 1991). The latter is a stable liquid, although highly acidic, and hence, has been neutralized with metal salts (eg. KOH) in fungicide formulations to avoid phytotoxicity (Dunhill, 1990). It dissociates in water into its metal cation and the active component, the phosphite anion (syn. phosphonate anion (HPO_3^{2-}) or hydrogen phosphonate ($H_2PO_3^-$)) (Dann & McLeod, 2021). The initial patent for a phosphonate fungicide was granted to Fosetyl-Al (Aliette WP), the aluminium salt of ethyl hydrogen phosphonate (Guest & Grant, 1991). The discovery that the phosphite anion was the actual active component of these products, led to the preferential use of simpler, more affordable salts of phosphonic acid that lacked the alkyl group (Bompeix & Saindrenan, 1984; Fenn & Coffey, 1984, 1985; Bower & Coffey, 1985; Coffey & Joseph, 1985; Dolan & Coffey, 1988; Guest & Grant, 1991). These include potassium phosphonate (a combination of potassium hydrogen phosphonate (KH_2PO_3) and dipotassium phosphonate (K_2HPO_3), sodium phosphonate, and ammonium phosphonate, all referred to as salts of phosphonic acid (Dann & McLeod, 2021). Phosphonates have traditionally been used for the management of oomycetes although they have also found application in the management of bacterial and fungal plant pathogens (Dempsey et al., 2018; Keča et al., 2018; Wen et al., 2009; Yogev et al., 2006), as plant fertilisers and biostimulants (Thao & Yamakawa, 2009), and as herbicides. Still, the latter three roles require further investigation (Dann & McLeod, 2021).

Although phosphonates were recently re-classified from Fungicide Resistance Action Committee (FRAC) code U33 (unknown mode of action) to P07 (host plant defence induction) (Fungicide Resistance Action Committee, 2022), their exact mode of action remains unknown (Dann & McLeod, 2021). It has been proposed that it involves pathogen inhibition by direct fungistatic action, the direct stimulation or priming of host plant defences, and pathogen stimulation to release stress metabolites that elicit a plant defence response (Dann & McLeod, 2021; Fenn & Coffey, 1987; Guest & Grant, 1991). Although it is known that phosphite has a direct fungistatic effect on oomycetes in vitro, possibly by interfering with phosphate and glucose metabolism and cell wall and cytoskeleton synthesis (King et al., 2010; McDonald et al., 2001), it has been difficult to prove such an effect *in planta*. Phosphite treatment of *P. palmivora* in vitro, altered phosphorylated metabolites including reduced nucleoside triphosphates, nucleoside diphosphate glucose, and soluble P, and increased phospholipids and polyphosphates, thereby inhibiting mycelial growth (Niere et al., 1990). Accordingly, it is proposed to interfere with P metabolism (McDonald et al., 2001). The in vitro sensitivity to phosphonates can be affected by the phosphate concentration of the growth media (Bompeix & Saindrenan, 1984; Fenn & Coffey, 1984; Guest & Grant, 1991). Phosphite is taken up by the phosphate transport system of *Phytophthora* in vitro, and phosphate in the growth media has been found to compete with and inhibit the uptake of phosphite (Fenn & Coffey, 1984; Griffith et al., 1989). Consequently, growth inhibition studies are generally conducted on media with low phosphate concentrations such as cornmeal agar (CMA) or modified Ribeiro's medium with phosphate concentrations of 0.38 mM and 0.084 mM, respectively (Bompeix & Saindrenan, 1984; Coffey & Bower, 1984). Therefore, in vitro and *in planta* phosphite concentrations necessary for inhibition, cannot simply be correlated. Additional factors that can influence inhibition in vitro include the media composition, the developmental stage of the pathogen, genomic make-up, previous fungicide exposure and geographic origin of strains tested, and whether liquid or solid culture media is used (Guest & Grant, 1991; Riley et al., 2024). Responses of host and pathogen *in planta* could be alterations in chemical or structural aspects, including the formation of protective layers and modifications in the composition and structure of the cell wall (Ramallo et al., 2019). Furthermore, the exact *in planta* intracellular localisation of phosphite remains unclear, although it is suspected to be in vacuoles in phosphate-abundant conditions, and in the cytoplasm during phosphate shortages (Danova-Alt et al., 2008). Phosphite concentrated in the cytoplasm might be more toxic to the pathogen (Dann & McLeod, 2021). A possible strategy for demonstrating a direct mode of action for phosphonates *in planta* involves infecting plants with isolates with different levels of in vitro sensitivity that are similar in other regards. A direct effect is demonstrated when the in vitro sensitive

isolates are more effectively controlled than the resistant ones by phosphonic acid treatment (Dann & McLeod, 2021). In a recent study, *P. citrophthora* isolates with different in vitro phosphonate sensitivities, caused different levels of brown rot, pre- and post-harvest, following potassium phosphonate treatment (Adaskaveg et al., 2017). Similarly, the discovery of a *P. citrophthora* isolate with reduced in vitro phosphonate sensitivity that translated into reduced brown rot control in the field, led to the conclusion that direct pathogen inhibition was the underlying mechanism of action. It was reasoned that, if an enhanced host defence response was responsible, *in planta* control would have been equally successful for the in vitro resistant and susceptible isolates, which was not the case (Hao et al., 2020). Although positive correlations between in vitro and *in planta* phosphonate sensitivities of *Phytophthora* species have been found (Bower & Coffey, 1985; Dolan & Coffey, 1988), solely attributing this to a direct *in planta* effect is not possible as plant defence induction could also possibly play a role (Dann & McLeod, 2021). Higher tissue phosphite concentrations could result in an amplified host defence response, as found with other plant resistance inducers (Gozzo & Faora, 2013).

In a manner akin to other plant resistance activators, phosphonic acid stimulates host plant resistance by inducing phytohormone production, leading to the activation of defence-related genes and proteins (Bürger & Chory, 2019; Dann & McLeod, 2021). Both salicylic acid (SA)- and jasmonic acid (JA)-responsive defence genes were upregulated in phosphite-treated, non-inoculated *Arabidopsis thaliana* plants (Eshraghi et al., 2011). The activation of both phytohormone pathways, often perceived as antagonistic (Thatcher et al., 2005), points to a complex, coordinated defence response primed by phosphite (Eshraghi et al., 2011). Studies on potatoes, utilising microarray and proteomic analysis, found a large number of differentially regulated genes between phosphite-treated and untreated plants in the absence of *P. infestans* inoculation. However, when phosphonic acid-treated plants that were inoculated were compared to untreated and inoculated plants, the number of differentially regulated genes and proteins was much lower (Burra et al., 2014; Feldman et al., 2020; Lim et al., 2013), suggesting that only a small number of genes that are differentially regulated in response to phosphonic acid are involved in resistance and/or, that priming occurs in response to phosphonic acid, allowing for a stronger immune response upon infection (Eshraghi et al., 2011; Feldman et al., 2020; Lim et al., 2013). Responses primed by phosphonic acid include the accumulation of ROS and phenolic compounds and the deposition of callose, culminating in an HR-like reaction that causes localised cell death (Daniel & Guest, 2006; Eshraghi et al., 2011; Lim et al., 2013; Machinandiarena et al., 2012). Reactive oxygen species induce systemic acquired resistance (SAR), an immune response against biotrophs and hemibiotrophs, modulated primarily by salicylic acid (Bürger & Chory, 2019). Gene expression and defence-deficient mutant studies have discovered multiple potential phosphite targets in plants, including the salicylic acid-responsive genes, mitogen-activated protein kinase MPK4, the transcriptional coactivator, NPR1 (known as the master regulator of SA signalling), and the WRKY transcription factor (Bürger & Chory, 2019; Machinandiarena et al., 2012; Massoud et al., 2012; Molina et al., 1998).

The phosphite dosage determines whether its action on *Phytophthora* species is primarily direct or indirect. Higher phosphite concentrations are associated with better disease control, primarily by direct fungistatic action, whereas lower concentrations are mainly associated with host plant defence induction and less effective disease control (Dann & McLeod, 2021). Roots of *Eucalyptus marginata*, inoculated with *P. cinnamomi* shortly after phosphonic acid application, developed larger lesions than those inoculated later after application. The former treatment was associated with low root phosphite concentrations and high levels of phenolics and enzyme activity involved in phytoalexin synthesis. In contrast, the latter treatment had higher root phosphite concentrations and low levels of defence markers (Jackson et al., 2000). In another study, different potassium phosphite dosages were compared for the control of *Hyaloperonospora arabidopsidis* in wild-type (WT) and mutant *Arabidopsis*, unable to accumulate salicylic acid. At high doses, the defence-deficient mutants demonstrated disease control as effective as the WT, whereas, at lower phosphonic acid concentrations, disease control was lost in the mutant. Furthermore, higher dosages resulted in better disease control than lower dosages in the WT (Massoud et al., 2012). More evidence of a concentration-dependent mode of action came from a study that investigated

the effect of phosphite concentration on the potato—*P. infestans* pathosystem. Potato plants, of which half the leaves were covered with plastic bags to prevent direct exposure to phosphite, were sprayed, resulting in high phosphite concentrations in uncovered leaves and low concentrations in the covered ones. Subsequent inoculation with *P. infestans* resulted in much higher disease severity in the covered leaves versus their uncovered counterparts. It was concluded that a direct mode of action was mainly responsible for disease control. It was reasoned that if an indirect effect was responsible for disease control, the covered leaves would have developed few symptoms like the uncovered ones. In addition, disease control in transgenic potato lines deficient in salicylic- or jasmonic acid production was not affected by the high phosphonic acid dose, further indicating a direct mode of action (Burra et al., 2014). Contemporary evidence suggests that high tissue concentrations of phosphite are necessary for effective disease control during periods of high disease pressure and inoculum load. Lower tissue concentrations could contribute to disease control during periods of lower disease pressure by inducing host defences (Dann & McLeod, 2021). However, as with other plant defence inducers, disease control varies with the environment, crop genetics, nutrition and healthy status, disease pressure, and the level of pre-induced plant defences (Gozzo & Faora, 2013; Walters et al., 2013; Reglinski et al., 2014).

The uptake of phosphonic acid affects phosphate metabolism within oomycete mycelia, leading to altered surface membrane and cell wall constituents of mycelia (Smillie et al., 1990), as well as increased secretion of elicitors, as has been found for *P. capsici* and *P. cryptogea* (Perez et al., 1995; Rouhier et al., 1993; Wilkinson et al., 2001a). Altered microbe-associated molecular patterns (MAMPs) can be recognised by pattern-recognition receptors (PRRs) of the host, triggering the host's innate immune response, known as PAMP-triggered immunity (PTI) (Bürger & Chory, 2019; Jones & Dangl, 2006). Furthermore, phosphonates can induce the release of effectors and elicitins from oomycetes that can trigger a host defence response (Wang et al., 2019). PAMP-triggered immunity involves various host responses, including an oxidative burst due to the production of ROS, an influx of calcium, mitogen-activated protein kinase (MAPK) cascade activation, a nitric oxide (NO) burst, the production of ethylene, the deposition of callose at cell walls, and the activation of defence response genes involved in immunity (Boller & Felix, 2009; Dalio et al., 2017. In addition to PAMP-triggered immunity (PTI), there is another type of plant defense known as effector-triggered immunity (ETI). ETI occurs when specific interactions between pathogen effectors (which come from avirulence or Avr genes) and resistance proteins (produced by resistance or R-genes) take place (Dalio et al., 2017; Flor, 1971). Effectors are molecules associated with or released by pathogens that can alter host cell structures and functions to facilitate infection and immune suppression (Göhre & Robatzek, 2008). Effectors either act in the intercellular space, where they are known as apoplastic effectors, or intracellularly, where they are called cytoplasmic effectors (Djamei et al., 2011; Kamoun, 2006). Both apoplastic and cytoplasmic effectors are produced by *P. nicotianae* (Dalio et al., 2017). The former includes elicitins such as parasiticein, known to be involved in the HR and possibly also with membrane remodelling (Kamoun et al., 1993; Nespoulous et al., 1999; Panabières et al., 2016). A positive correlation has also been found between the upregulation of elicitin expression and tissue necrosis in the latter stages of infection in the *P. nicotianae*-citrus pathosystem (Boava et al., 2011). Other apoplastic effectors of *P. nicotianae,* possibly involved in citrus infection, include necrosis-inducing *Phytophthora* protein 1 (NPP1), necrosis and ethylene-inducing peptide 1 (NEP1)-like protein, the apoplastic polygalacturonases, and cellulose-binding elicitor and lectin activity (CBEL), all likely involved in the HR and/or tissue necrosis (Fellbrich et al., 2002; Khatib et al., 2004; Wu et al., 2008). Cytoplasmic effectors of *P. nicotianae,* such as RxRL and Crinkler effectors (CRNs), are known to interfere with host plant physiology, such as auxin production, and suppress plant immunity, respectively (Evangelisti et al., 2013; Mafurah et al., 2015). Filtrates of *P. capsici* and *P. cryptogea* cultures, grown in the presence of phosphonic acid, were found to contain high levels of the elicitins, capsicein and cryptogein, respectively (Perez et al., 1995), while *P. cinnamomi* grown in the presence of phosphonic acid in vitro, overexpressed a presumed phosphoproteoglycan (Wong et al., 2009). Furthermore, filtrates of *Phytophthora* cultures, grown in low phosphonic acid concentrations, demonstrated enhanced elicitation of host plant defences (Rouhier et al., 1993; Saindrenan et al., 1990).

Phosphonic acid can also influence oomycete-inhibiting endophytes and microbiomes of the rhizosphere and phylloplane (Cohen & Coffey, 1986). It can stimulate or inhibit root colonisation by mycorrhiza (Howard et al., 2000; Jabaji-Hare & Kendrick, 1987; Seymour et al., 1994; Sukarno et al., 1998), which can have a suppressive effect on plant pathogens (Baum et al., 2015). The effect of phosphonic acid on these microbial communities can be either direct, due to its antimicrobial activity (Bultreys et al., 2018), or indirect, through host plant defence induction or possibly by altering plant exudates (Carvalhais et al., 2013). Ultimately this can indirectly affect *Phytophthora* species infection and colonisation (Dann & McLeod, 2021).

Phosphonic acid is taken up by the plant's phosphate transport system and is ambimobile, meaning it is systemically transported in both the xylem and phloem (Dann & McLeod, 2021; Guest & Grant, 1991; Guest et al., 1995). It can be applied to the roots (soil drench), leaves (foliar spray), or trunk (spray/paint/injection) (Guest et al., 1995; Nyoni et al., 2019; Taylor et al., 2011). Its high solubility and chemical stability in water account for its efficient movement, both acropetally and basipetally (Whiley et al., 1995). Translocation is influenced by the physiological sink strengths during application and hence, will accumulate in the most physiologically active (i.e., growing) tissues during that time (Guest et al., 1995; Nartvaranant et al., 2004; Whiley et al., 1995), following the seasonal movement of carbohydrates such as occurs during root flushes (Graham, 2011). Therefore, phosphonate applications should be timed to coincide with root flush periods that occur during the rainy season (Dewdney & Johnson, 2022; Graham & Feichtenberger, 2015; Le Roux, 2003; Nyoni et al., 2021). Although phosphonates are known to have both preventative and curative action (Hao et al., 2020), evidence suggests that preventative application is more effective at reducing *Phytophthora* disease severity in citrus (Sandler et al., 1986).

The plant tissue phosphite concentration has been used in various studies to evaluate the efficacy of phosphonate treatments and application methods, yielding significant correlations in some but not in others (El-Hamalawi et al., 1995; Shearer & Crane, 2012; Smillie et al., 1989; Wilkinson et al., 2001a). The threshold root phosphite concentration for the effective control of Phytophthora root rot of citrus is yet to be determined. The maintenance of this threshold concentration is also important as phosphonates are fungistatic and hence, once the concentration drops below this value, the pathogen can once again become active (Wilkinson et al., 2001b, c). Orbovic et al. (2008) determined root phosphite concentrations following soil and foliar applications on sweet orange (*C. sinensis* (L.) Osbeck) seedlings and found the former method to result in significantly higher concentrations than the latter. This translated into significantly better Phytophthora root rot control with soil drench compared to foliar application, although the latter method still resulted in significantly better control than untreated plants. Besides its effect on disease severity, soil drench application can also significantly reduce *Phytophthora* soil inoculum levels, suggesting a direct mode of action (Belisle et al., 2019; Hao et al., 2019). However, soil drench application of fosetyl-Al was found to be phytotoxic to citrus, although it still reduced soil propagule densities (Timmer et al., 1998). Schutte et al. (1991) measured root phosphite concentrations in citrus by gas–liquid-chromatography following trunk injection, trunk paint, and foliar sprays of phosphonates. They found trunk paints resulted in the most rapid accumulation of phosphite in the roots, followed by foliar sprays, with concentrations peaking at 21- and 28 days post-application respectively. However, for the former method, phosphite concentrations subsequently declined to negligible levels by 42 days, whereas paints and trunk injection, resulted in higher root phosphite concentrations that persisted for longer than 42 days. For all application methods, root phosphite levels had declined to negligible levels by 63 days post-application. This study concluded that application intervals should not exceed 42 days for any application method. Trunk applications are labour-intensive and expensive due to high labour costs in South Africa and can potentially cause tree injury (McLeod et al., 2018). McLeod et al. (2018) determined root phosphite concentrations by high-performance liquid chromatography-mass spectroscopy (LC–MS/MS) following various application methods on avocados (*Persea americana* Mill.) to evaluate their efficacy for controlling root rot caused by *P. cinnamomi.* Foliar sprays of potassium- or ammonium phosphonate and trunk injection of potassium phosphonate were compared. Foliar sprays of ammonium- or potassium phosphonate resulted in root phosphite concentrations similar to that achieved

by trunk injection and therefore, can be considered a viable alternative application method (McLeod et al., 2018).

It is known that root phosphite concentrations in perennials decrease over time, although the underlying mechanism is unclear (Dunhill, 1990; McDonald et al., 2001). There is no evidence that plants metabolise phosphite (Dann & McLeod, 2021). The decrease in phosphite concentration in roots may due to a dilution effect from plant growth, exfoliation, fruit harvest, and leaching from roots into the soil (Kumar et al., 2009; McLeod et al., 2018; Nyoni et al., 2021). Furthermore, little is known about the storage and re-translocation of phosphites in perennials. In avocados, phosphite initially moves acropetally to the leaves, from where it is translocated basipetally to the roots and a lesser extent, the bark and trunk wood (Masikane et al., 2020; Whiley et al., 1995). Phosphite residues have been found in the fruits and other tissues of avocado and apple trees two years after application (Malusà & Tosi, 2005; Masikane et al., 2020). Maximum residue levels (MRLs) in fruits are enforced for phosphonic acid-based fungicides (Dann & McLeod, 2021). These levels vary between crops and among countries. In the US, the salts of phosphonic acids, but not fosetyl-Al, are exempt from these requirements (USEPA, 2000, 2018). In contrast, the European Food Safety Authority (EFSA) and the Joint Meeting on Pesticide Residues (JMPR) do recommend the enforcement of MRLs for all phosphonic acid-based fungicides (EFSA, 2005, 2012, 2013, 2018, 2020; FAO/WHO, 2019). Phosphonates are generally environmentally friendly with low mammalian toxicity (Guest & Grant, 1991). Toxicological assessments of fosetyl-Al have not found any carcinogenic, genotoxic (mutagenic), teratogenic, or neurotoxic effects at levels below the acceptable daily intake (ADI), and it is rapidly eliminated from the body (EFSA, 2018; FAO/WHO, 2018). The phosphonic acid salts (potassium, sodium, and ammonium phosphonate) have toxicological profiles similar to fosetyl-Al (EFSA, 2012, 2013; FAO/WHO, 2018). Furthermore, phosphonates show no acute toxicity, averting the need for acute reference dosages (ARfDs) (Dann & McLeod, 2021).

Phosphite is also used as a fertiliser despite being an inferior phosphorous source than phosphate and its direct nutritional value to plants being unknown (Rickard, 2000; Rothbaum, 1964). Notwithstanding, foliar applications of potassium phosphite were shown to restore normal growth in phosphorous-deficient citrus trees and enhance fruit quality and yield (Albrigo, 1999; Lovatt, 1999). However, its effectiveness as a phosphorous source is still disputed due to its slow conversion to phosphate in plants by non-enzymatic oxidation (Smillie et al., 1988; Guest & Grant, 1991; César Bachiega Zambrosi et al., 2011). This occurs over the course of months in citrus, which explains its long residual activity (Graham, 2011; Guest & Grant, 1991). Consequently, phosphite can be phytotoxic if applied too frequently or at too high a rate (César Bachiega Zambrosi et al., 2011). Conversely, when applied to the soil, microorganisms oxidise it to phosphate, which can then be utilised as a phosphorous source by plants (Adams & Conrad, 1953; Casida, 1960; Guest & Grant, 1991; Malacinski & Konetzka, 1966). Soil drench applications of phosphite or phosphate nutrient solutions did not differ significantly in terms of their growth-promoting effects on citrus seedlings. This effect was attributed to the oxidation of phosphite to phosphate by soil microorganisms and a lesser extent, to abiotic oxidation (Orbovic et al., 2008). However, even this is considered too slow to be a sufficient phosphorous source for plants, according to McDonald et al. (2001). Furthermore, phosphite applied to phosphate-deficient soils at rates inhibitory to *Phytophthora* species can be phytotoxic as it inhibits the plant's phosphate starvation response (McDonald et al., 2001; Thao & Yamakawa, 2009). Notwithstanding, the phytotoxicity of potassium phosphonate is generally very low (Guest & Grant, 1991).

Phosphonate resistance in *Phytophthora*

Although resistance can develop to all fungicides, the risk varies based on the fungicide class. Site-specific fungicide classes have a much higher risk of resistance evolving than multisite classes (Corkley et al., 2022). Phosphonates are classified as low risk to resistance development (Fungicide Resistance Action Committee, 2022). Despite this, *Phytophthora* species with reduced sensitivity have been reported including *P. capsici* to potassium phosphonate and *P. cinnamomi* to fosetyl-Al, phosphorous acid, and potassium phosphite (Belisle et al., 2019; Dobrowolski et al., 2008; Duvenhage, 1994; Fenn & Coffey, 1987; Veena

et al., 2010; Wilkinson et al., 2001a). There have also been reports of reduced sensitivity to potassium phosphite in citrus isolates of *P. nicotianae*, *P. citrophthora*, and *P. syringae* (Kleb.) Kleb. (Adaskaveg et al., 2017; Hao et al., 2020). A recent study of *Phytophthora* isolates from Californian citrus orchards found the vast majority of *P. nicotianae* (86.8%) and a small percentage of *P. citrophthora* (16.9%) and *P. syringae* (21.7%) to have reduced in vitro sensitivity to potassium phosphite, as determined by an agar dilution method. Potassium phosphite concentrations necessary for 50% inhibition of growth (EC_{50}) ranged from 12.2–122.8 µg/mL, 4.6–299.6 µg/mL, and 8.5–162.4 µg/mL for *P. nicotianae, P. citrophthora,* and *P. syringae* respectively, with means of 64.1 µg/mL, 20.4 µg/mL, and 23.9 µg/mL. This translated into reduced brown rot control when caused by a resistant isolate of *P. citrophthora*, demonstrating the potential risk of field resistance developing to this fungicide (Hao et al., 2020). Similarly, Adaskaveg et al. (2017) determined EC_{50} values for potassium phosphite among Californian citrus isolates of *P. citrophthora, P. syringae,* and *P. nicotianae*, and found them to range from 5.5 to 252 µg/mL, 9.8–141.6 µg/mL, and 12.2–141.5 µg/mL, respectively. Riley et al. (2024) found moderate to full resistance to potassium phosphite in isolates of *P. syringae* (EC_{50} values between 25 and 75 µg/mL) and *P. citrophthora* (EC_{50} values up to 13.69 µg/mL), respectively.

Baseline sensitivity studies were rarely conducted before the registration or adoption of new products (Adaskaveg et al., 2017). This is important as populations are expected to show diversity in sensitivity as with other traits (Guest & Grant, 1991). Therefore, it is not known whether resistant isolates have arisen from mutations or the selection of naturally resistant strains in the population (Dann & McLeod, 2021). Despite these findings, phosphonic acid is still used successfully against brown rot in South Africa (Dann & McLeod, 2021). To ensure that phosphonates remain effective, resistance management strategies should include using new fungicides in rotations or mixes with phosphonates (Corkley et al., 2022). Recently, four such new fungicides namely, oxathiapiprolin (an oxysterol-binding protein inhibitor; FRAC code 49), mandipropamid (a carboxylic acid amide; FRAC code 40), ethaboxam (a thiazole carboxamide; FRAC code 22), and fluopicolide (a benzamide; FRAC code 43), demonstrated superior control of citrus root rot and *Phytophthora* species soil populations than potassium phosphonates and mefenoxam in greenhouse and field trials (Hao et al., 2019).

Fitness of fungicide-resistant isolates

Fitness is an organism's ability to contribute to the gene pool in future generations. It is determined by quantifying parameters related to pathogenicity and reproductive ability or the actual pathogen populations after competing in coinfections *in planta* (Hu et al., 2008). Information on the fitness of resistant isolates relative to their susceptible counterparts is important for resistance management decisions (Hu et al., 2008). The development of fungicide resistance in a strain can come at the expense of its ability to survive, reproduce, and compete with other strains without fungicide exposure if the resistance mechanism disrupts physiological or biochemical functions. This is known as a fitness cost (Hawkins & Fraaije, 2018; Zhan & McDonald, 2013). Various mechanisms underlie fitness costs, including reduced activity or efficacy of mutated target sites and resource allocation costs from the over-expression of targets or an up-regulation in active transport (Hawkins & Fraaije, 2018). The fitness consequences of resistance mutations are influenced by epistatic effects of the genetic background, for example, compensatory mutations in other genes that can offset the burden caused by the initial resistance mutation (Corkley et al., 2022; Hawkins & Fraaije, 2018). In some instances, compensatory mutations can allow mutants with fitness penalties to become established in the population (Lalève et al., 2014). An evolutionary trade-off between the advantages of resistance versus its fitness cost can affect whether resistance becomes established in the population (Hawkins & Fraaije, 2018; Zhan & McDonald, 2013). Under non-selective conditions, such as periods devoid of fungicide exposure, a fitness cost can prevent the establishment of resistance. Therefore, given adequate time between fungicide treatments, resistance evolution can be reversed (Hawkins & Fraaije, 2018). Conversely, resistant mutants that don't carry fitness costs will persist, rendering the fungicide permanently ineffective (Zhan & McDonald, 2013). It follows that fitness costs have implications for resistance management

strategies (Hawkins & Fraaije, 2018). Moreover, it is important for resistance risk assessment of fungicides (Hollomon, 2015). If not considered, the risk can easily be overestimated. Conversely, overestimating the impact of fitness penalties can increase the risk of resistance developing if, for example, compensatory mutations arise or the temperatures in the field differ from those under which the fitness cost is expressed (Hawkins & Fraaije, 2018).

The molecular mechanisms underlying resistance determine the type of fitness cost. Target site mutations conferring resistance by reducing fungicide binding to targets, such as enzymes, can come at the expense of enzyme function (Cools et al., 2013). Point mutations can also result in increased enzyme activity, conferring a type of metabolic resistance, although potentially at the expense of protein stability (Wang et al., 2002). Negative cross-resistance is another potential consequence of a target site mutation. This is the phenomenon by which a resistance mutation to one agent results in a fitness cost in the presence of another agent (Cools et al., 2010). Conversely, target site overexpression might cause positive cross-resistance to all members of a particular MoA (Cools et al., 2012). Overexpression can also compensate for functional constraints caused by a target site mutation, thereby changing the fitness penalty from a functional trade-off to an allocation cost (Bean et al., 2009; Hawkins & Fraaije, 2018). Metabolic circumvention, by bypassing an inhibited catalytic step in a metabolic pathway, can come at a cost, as the alternative pathway is usually less efficient (Wood & Hollomon, 2003). The constitutive over-expression of target sites, detoxifying enzymes, or efflux pumps confers resistance at the expense of resources that could have been used for growth and reproduction. This is called a resource allocation cost (Walters & Boyle, 2005). Constitutive over-expression can also cause the excessive accumulation of protein and reduced regulatory control, resulting in a fitness cost (Hawkins & Fraaije, 2018; Weinstein & Solomon, 1990). The occurrence of de novo resistance mutations can increase the frequency and decrease the diversity of linked genes in a selective sweep (Brunner et al., 2014). This can come at a fitness cost if the linked alleles are detrimental or if useful alleles that confer a selective advantage under different conditions are lost from the population (Hawkins & Fraaije, 2018).

Fitness costs can be measured in competition assays consisting of mixed infections with resistant and sensitive strains or by measuring individual components of fitness such as sporulation, mycelial growth, aggressiveness, and incubation period (Billard et al., 2012; Fillinger et al., 2012; Hawkins & Fraaije, 2018; Zhan & McDonald, 2013). Competition assays give a more accurate representation of fitness costs where mixed infections occur regularly in the field (Hawkins & Fraaije, 2018). They measure the change in relative frequencies of pathogen strains over time in mixed experimental populations. This is then used to estimate a parameter known as the selection coefficient, which is a measure of the difference in fitness between two strains in coinfection (Zhan & McDonald, 2013). It is the most inclusive measure of pathogen competitive ability, as it combines all aspects of pathogen fitness across the infection cycle, including penetration, colonization, reproduction, and dispersal into a single parameter (Antonovics & Alexander, 1989; Lannou & Mundt, 1996; Zhan & McDonald, 2013). There are three prerequisites to using selection coefficients to quantify competitive ability. Firstly, the relative frequencies of the strains should be known at, not less than two time points to have at least an initial and final frequency (Sommerhalder et al., 2011; Zhan et al., 2002). Secondly, the number of generations of pathogen reproduction between time points should be known. This can be estimated for many pathogens that require specific environmental conditions to complete a reproductive cycle, for example, through the use of climatic data from the experimental site (Zhan & McDonald, 2013). Lastly, the strains should be unmistakably differentiated from one another, usually by molecular genetic markers, as done in mark-release-recapture experiments (Abang et al., 2006; Sommerhalder et al., 2011; Zhan et al., 2002), and large enough samples should be taken to obtain accurate estimates of genotype frequencies (Zhan & McDonald, 2013).

Fitness costs can be measured in laboratory and field-based experimental evolutionary studies, the latter providing a more realistic assessment due to fluctuating environmental conditions that can affect competition between strains (Zhan & McDonald, 2013). However, it also has the most uncontrolled variables, including temperature and the genetic background of strains, which can vary and influence fitness costs (Hawkins & Fraaije, 2018). Below field trials on a

scale of inclusive measures of fitness, are glasshouse trials, which provide a more controlled environment, including climate and genetic background of isolates (since the use of isogenic transformants or mutants is permitted) (Arabiat et al., 2017; Scalliet et al., 2012). However, they sometimes do not include the entire life cycle of the pathogen, such as overwintering stages (Hawkins & Fraaije, 2018). At the other end of the spectrum, in terms of inclusive measures of fitness and control of confounding variables, are in vitro assays. These are limited to a few individual measures of fitness, such as hyphal growth and asexual spore production, and can be unreliable as certain rich media may compensate for and therefore mask fitness costs (Hawkins & Fraaije, 2018).

Fitness costs vary under different environmental conditions, host genetics, pathogen life stages, and genetic backgrounds in which the mutation occurs (Hawkins & Fraaije, 2018; Kawecki & Ebert, 2004; Zhan & McDonald, 2013). Consequently, experiments have yielded inconsistent findings of fitness costs associated with fungicide resistance. Nowhere is this more apparent than with phenylamide resistance in *Phytophthora* species. In replacement series experiments that investigated the relative competitive ability of metalaxyl-resistant strains of *P. nicotianae,* resistant strains were found to be no less fit than their sensitive counterparts in the absence of fungicide exposure, suggesting that resistance will remain if metalaxyl use is discontinued (Timmer et al., 1998). Hu et al. (2008) compared the reproductive ability, pathogenicity, and relative competitive ability of mefenoxam-resistant- and sensitive isolates of *P. nicotianae* and found the former to be fitter than the latter. It was concluded that resistant strains would persist in the population, even in the absence of mefenoxam. Similarly, mefenoxam resistance in *Phytophthora erythroseptica* strains was not associated with a fitness cost, based on results from coinfection experiments (Chapara et al., 2011), while mefenoxam-resistant isolates of *P. capsici* from peppers and squash, did not differ significantly from sensitive ones in terms of in vitro mycelial growth rate and sporangium production capacity, and *in planta* disease severity (Café-Filho & Ristaino, 2008). Conversely, metalaxyl-insensitive isolates, produced by successive subculturing on metalaxyl-amended media, showed reduced colony growth rates on unamended media compared to their sensitive parent counterparts. Furthermore, the insensitive isolates reverted to sensitivity after successive subculturing on unamended media (Bruin & Edington, 1981). A similar observation was made for Carboxylic Acid Amide-resistant mutants of *Phytophthora litchii* that reverted to sensitivity after 11 successive generations in the absence of the fungicide. These mutants also showed reduced mycelial growth, sporulation, and aggressiveness compared to their wild-type parent strain (Wang et al., 2010). Fitness costs have also been reported for an azoxystrobin-resistant *Magnaporthe oryzae* strain (Ma & Uddin, 2009), as well as for demethylation inhibitor-resistant *Cercospora beticola* strains (Karaoglanidis et al., 2001). Studies investigating fitness costs for phosphonate resistance are scarce. A single study compared a phosphorous acid-resistant mutant strain of *P. capsici* to its wild-type parent and found no significant differences in growth- and sporulation rates or pathogenicity on pepper plants. The resistant strain was also isolated at a higher frequency from infested soil than its wild-type parent. Furthermore, resistance remained stable after serial subculturing on non-amended media. These results suggested that no fitness penalty was associated with phosphorous acid resistance (Lucas et al., 1990).

The absence of a fitness cost can have various underlying reasons. The resistance-conferring mutation could affect a gene not involved in pathogen fitness (Zhan & McDonald, 2013). Alternatively, duplication of an allele with a resistance-conferring mutation might allow it to maintain its original function if one of the copies remains wild-type (Qutob et al., 2009; Ridout et al., 2006; Tian et al., 2011). In other cases, a fitness cost might be too small to detect in field trials when background variance results in high experimental error (Zhan & McDonald, 2013). The failure to find a fitness cost might also be due to measuring the wrong fitness component as not all might be affected by the resistance-conferring mutation (Zhan & McDonald, 2013). Compensatory mutations might also mask fitness costs (Collmer, 1998; Leach et al., 2001).

Conclusion

To ensure the continued competitiveness of the South African citrus industry, updated knowledge of

Phytopthora species is required for the effective management thereof. Phosphonates form an integral part of the chemical arsenal against this pathogen. However, recent reports of *Phytophthora* species with reduced phosphonate sensitivity are disconcerting, and warrant continued investigations into the sensitivity of *P. nicotianae* and *P. citrophthora* from citrus production regions to establish whether the current dosage rates of phosphonates are still effective. In a world where 'harder' chemistries are progressively being phased out, prolonging the effective life of phosphonates is crucial. Resistance management strategies, governed by evolutionary principles, that take fitness costs into account, can aid in achieving this goal. However, there is a knowledge gap in terms of the current sensitivity of *Phytophthora* isolates from citrus towards phosphonates and the fitness costs associated with reduced phosphonate sensitivity, which represents a research opportunity.

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Declarations

Competing interests The authors declare no competing interests.

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