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REVIEW ARTICLE

A review of knowledge on the mechanisms of action of the rare sugar D-tagatose against phytopathogenic oomycetes

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Abstract

D-tagatose is a rare monosaccharide, naturally present at low concentrations in some fruits and dairy products. D-tagatose is "generally recognized as safe" and is used as a low-calorie sweetener in the food industry. It is able to inhibit the growth of numerous microorganisms, such as phytopathogenic oomycetes responsible for important crop diseases. Thanks to the negligible effects on human health and the environment, D-tagatose has been proposed as a sustainable product for crop protection. This review describes the current knowledge on modes of action of D-tagatose against phytopathogenic oomycetes and its potential uses in agriculture. D-tagatose can negatively affect the growth of phytopathogenic oomycetes by inhibiting key enzymes of sugar metabolism, such as β-glucosidase in *Phytophthora infestans*, and fructokinase and phosphomannose isomerase in *Hyaloperonospora arabidopsidis*. Moreover, D-tagatose affects sugar content, causes severe mitochondrial alterations, and inhibits respiration processes with the accumulation of reactive oxygen species in *P. infestans*, but not in *P. cinnamomi*. Differential effects of D-tagatose are associated with a global gene downregulation in *P. infestans* and with an efficient transcriptional reprogramming of multiple metabolic processes in *P. cinnamomi*. D-tagatose displays possible species-specific effects in *Phytophthora* spp. and nutritional properties on some plant-associated microorganisms. However, inhibitory effects are reversible and *P. infestans* growth can be restored in the absence of D-tagatose. Further functional studies are discussed in this review, in order to promote the use of D-tagatose for sustainable crop protection.

KEYWORDS
mechanism of action, microbial growth inhibition, phytopathogenic oomycetes, rare sugar, tagatose

1 | INTRODUCTION

Rare sugars are defined as monosaccharides that exist only in a small amount in nature (Izumori et al., 2008). Rare sugars comprise 20 hexoses (D-allose, L-allose, D-altrose, L-altrose, L-fructose, L-galactose, L-glucose, D-gulose, L-gulose, D-idose, L-idose, L-mannose, D-psicose, L-psicose, D-sorbose, L-sorbose, D-tagatose, L-tagatose, D-talose, and L-talose) and nine pentoses (D-arabinose, D-lyxose, L-lyxose, L-ribose, D-ribulose, L-ribulose, L-xylose, D-xylulose, and L-xylulose), and most of them are isomers of the seven common monosaccharides that exist in large amounts in nature, L-arabinose, D-fructose, D-galactose, D-glucose, D-mannose, D-ribose, and D-xylose (Ahmed, 2001; Izumori et al., 2008; Jayamuthunagai et al., 2017). The biological properties of rare sugars are not fully understood and their promising applicative values are underestimated, mainly because of their limited available quantity in nature (Li et al., 2013; Mijailovic et al., 2021). However, the development of innovative enzymatic and microbial methods for rare sugar synthesis have lowered the cost of production and expanded their application in several scientific and technological areas of medicine, food, and agriculture (Granström et al., 2004; Li et al., 2013; Oh, 2007).

Among rare sugars, D-tagatose is naturally present at low concentrations in foods, such as apple, orange, milk, and cheese (Vastenavond et al., 2011). D-tagatose is also present as a metabolic intermediate of the tagatose-6-phosphate pathway, which is activated for the degradation of D-galactose and D-lactose in some bacteria, such as *Staphylococcus aureus* and *Streptococcus lactis* (Bissett & Anderson, 1974). D-tagatose is an epimer of D-fructose, with an inversion of the spatial configuration of the hydroxyl group of the fourth carbon (C4-OH group; Figure 1). D-tagatose can be synthesized from D-lactose in a two-step process, where D-lactose is enzymatically hydrolysed to D-glucose and D-galactose using lactase in the first step (Figure 2; Bertelsen et al., 1999). In the second step of the chemical synthesis, D-galactose is then isomerized to D-tagatose in the presence of calcium hydroxide (Bertelsen et al., 1999). Although chemical synthesis is an efficient method for the large-scale production of D-tagatose, consumer concerns and safety issues stimulated the development of processes based on biological synthesis (Roy et al., 2018). In particular, bacterial L-arabinose isomerase can be used for the isomerization of D-galactose to D-tagatose in the second step of the biological synthesis (Figure 2; Kim, 2004).

D-tagatose was "generally recognized as safe" by the Food and Drug Administration in the USA, because it has no negative impact on human health (Levin, 2002; Vastenavond et al., 2011). Thanks to its low caloric content (1.5 kcal/g) and small glycemic index compared to sucrose, D-tagatose is currently used in the food industry as a low calorie sweetener (Vastenavond et al., 2011). In addition, D-tagatose has shown therapeutic properties on human subjects and has been proposed to control type 2 diabetes, hyperglycaemia, anaemia, haemophilia, and obesity (Levin, 2002). D-tagatose affects the growth of some human-associated microorganisms and has prebiotic properties on the human gut microbiota, by increasing the abundance of beneficial bacteria (e.g., *Enterococcus* spp. and *Lactobacillus* spp.; Bautista et al., 2000; Bertelsen et al., 1999; Vastenavond et al., 2011) and

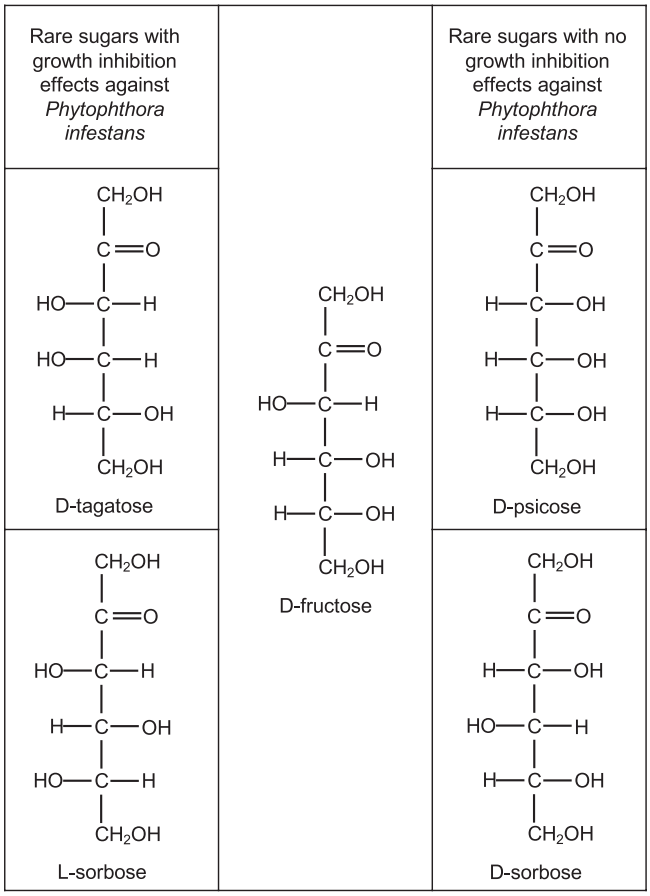

FIGURE 1 Fisher projections of some rare sugars. Fisher projections and inhibitory properties against *Phytophthora infestans* are reported for some rare sugars with structural similarities with D-fructose and potential applicative value. According to the protocol reported by Chahed et al. (2020), *P. infestans* growth was inhibited ($p \leq 0.05$; Kruskal–Wallis test) by 5 g/L D-tagatose (84.20 ± 0.23%; mean inhibition percentage and standard error compared to control samples) and 5 g/L L-sorbose (42.04 ± 0.12% this study), but it was not affected by 5 g/L D-psicose (0.22 ± 0.13%), 5 g/L D-sorbose (0.39 ± 0.15%), and 5 g/L D-fructose (0.19 ± 0.11%)

inhibiting the growth of some human pathogens (e.g., *Streptococcus mutans* and *Salmonella enterica* serovar Typhimurium; Hasibul et al., 2018; Lobete et al., 2017). D-tagatose can be used as a carbon source by only few microbial taxa, such as *Exiguobacterium* spp., *Lactobacillus* spp., and *Lactococcus* spp. (Martinussen et al., 2013; Raichand et al., 2012; Van der Heiden et al., 2013; Wu & Shah, 2017). In particular, the D-tagatose metabolism involves the tagatose-6-phosphate pathway in *Lactobacillus* spp. and *Lactococcus* spp. (Martinussen et al., 2013; Wu & Shah, 2017). D-tagatose incubation causes a complex transcriptional reprogramming of the carbohydrate metabolism in *L. rhamnosus* (Koh et al., 2013), indicating precise metabolic adaptations for the rare sugar catabolism in bacteria. On the other hand, D-tagatose is not catabolized by several human-pathogenic bacteria, such as *Bacillus cereus*, *Escherichia coli*, *Listeria monocytogenes*, *S. enterica* serovar Typhimurium, *S. aureus*, *Pseudomonas aeruginosa*, and *Yersinia enterocolitica* (Bautista et al., 2000), indicating antinutritional properties on specific microbial taxa. Likewise, D-tagatose inhibits the growth of

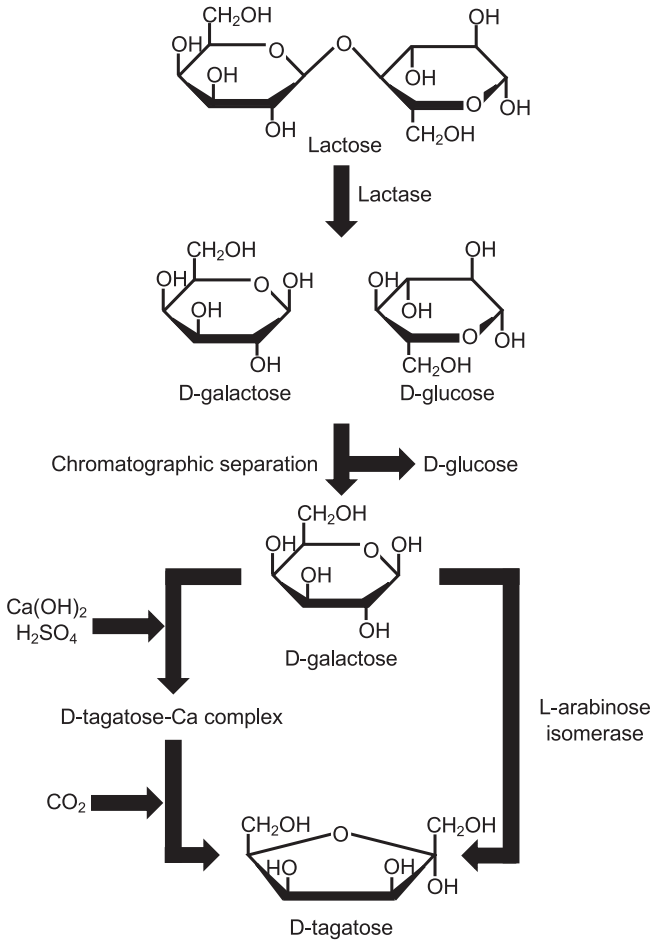

FIGURE 2 D-tagatose chemical and biological synthesis reactions. D-tagatose synthesis starts with the hydrolysis of lactose into D-glucose and D-galactose by lactase enzyme. In the chemical synthesis, D-galactose is then isomerized to D-tagatose with calcium hydroxide ($Ca[OH]_2$) and the reaction is stopped by adding sulphuric acid (H_2SO_4). The chemical process requires an additional reaction using carbon dioxide (CO_2). In the biological synthesis, D-galactose is isomerized to D-tagatose by L-arabinose isomerase. Synthesis reactions are summarized according to Bertelsen et al. (1999) and Kim (2004)

some phytopathogens and it has been proposed as a promising plant protection product (Chahed et al., 2020, 2021; Corneo et al., 2021b; Mijailovic et al., 2021; Mochizuki et al., 2020; Perazzolli et al., 2020). The aim of this review is to summarize the current knowledge on the modes of action of D-tagatose against phytopathogenic oomycetes and to propose further functional studies that will support the use of this rare sugar for sustainable crop protection.

2 | D-TAGATOSE INHIBITS THE GROWTH OF A WIDE RANGE OF PLANT PATHOGENS

D-tagatose inhibits the growth of a wide range of phytopathogens with negligible effects on human health and the environment (Ohara et al., 2008). For instance, D-tagatose controls grapevine powdery mildew (*Erysiphe necator*), tomato grey mould (*Botrytis cinerea*), alternaria sooty spot (*Alternaria brassicicola*), brown rust (*Puccinia recondita*), and rice sheath blight (*Rhizoctonia solani*) (Mochizuki et al., 2020; Perazzolli et al., 2020). Among phytopathogens, several oomycetes are inhibited by D-tagatose, such as *Hyaloperonospora arabidopsidis*, *Peronospora destructor*, *Peronospora farinosa*, *Phytophthora infestans*, *Plasmopara viticola*, *Pseudoperonospora cubensis*, *Pythium aphanidermatum*, and *Pythium graminicola* (Chahed et al., 2020; Corneo et al., 2021b; Mochizuki et al., 2020; Perazzolli et al., 2020). Disease control can be achieved by D-tagatose foliar spray, soil drenching, or seed treatment, and no phytotoxic effects are noticed on treated plants (Corneo et al., 2021a; Ohara et al., 2008). In addition, D-tagatose has both preventive and curative effects against some plant diseases, such as cucumber downy mildew (Mochizuki et al., 2020). Greenhouse and field trials showed that D-tagatose efficacy against downy mildew of grapevine, cucumber, Chinese cabbage, onion, and spinach is comparable to that obtained with chemical fungicides (e.g., chlorothalonil, copper, cyazofamid, metalaxyl, and mancozeb) (Mochizuki et al., 2020; Perazzolli et al., 2020), suggesting a great potential of this rare sugar to substitute synthetic chemical fungicides in crop protection.

D-tagatose has a double effect on plant health by acting as an antinutritional molecule on some phytopathogens (direct effect) and as a nutritional factor on some indigenous biocontrol microorganisms (indirect effect) (Perazzolli et al., 2020). In particular, D-tagatose treatments of grapevine decreases the relative abundance of *Erysiphe* spp., in agreement with the reduction of powdery mildew symptoms caused by *E. necator* (Perazzolli et al., 2020). On the other hand, D-tagatose exhibits a prebiotic effect on the phyllosphere microbiota and increases the relative abundance of some natural microorganisms with potential beneficial effects on grapevine (e.g., *Alternaria* spp., *Aureobasidium* spp., *Exiguobacterium* spp., and *Exophiala* spp.) that could partially contribute to disease control by competing for space and nutrients or by inducing plant resistance (Perazzolli et al., 2020).

3 | D-TAGATOSE HAS VARIOUS MECHANISMS OF ACTION AGAINST PHYTOPATHOGENIC OOMYCETES

The growth inhibition of phytopathogenic oomycetes caused by D-tagatose is associated with negative impacts on multiple metabolic and transcriptional processes (Figure 3; Chahed et al., 2020, 2021; Corneo et al., 2021b; Mochizuki et al., 2020). In particular, D-tagatose causes severe mitochondrial alterations in *P. infestans*, with the consequent decrease in ATP content, oxygen consumption rate, and mycelial growth (Chahed et al., 2020). Moreover, D-tagatose incubation causes the accumulation of reactive oxygen species (ROS) and upregulation of genes related to apoptosis and oxidative stress response in *P. infestans* (Chahed et al., 2020), indicating possible oxidative damage on cell structures. Similarly, the rare sugar L-sorbose affects the growth and morphology of *Neurospora crassa*

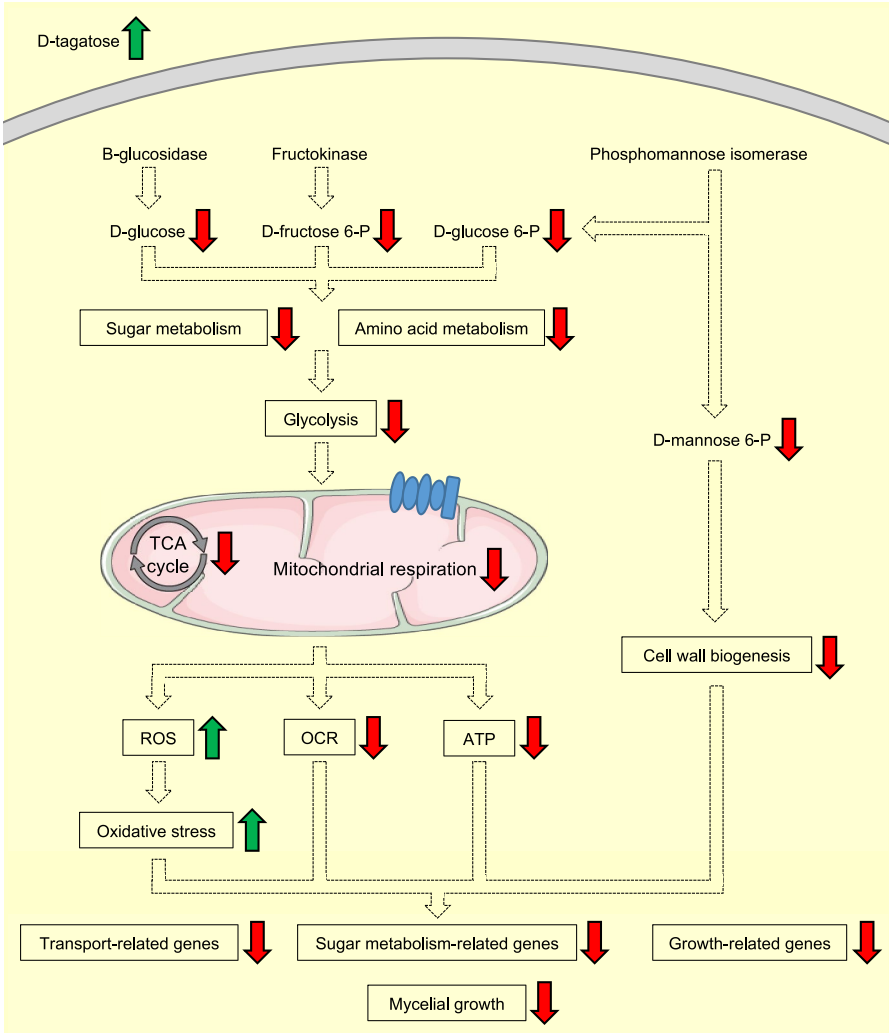

FIGURE 3 Possible mechanisms of action of D-tagatose against phytopathogenic oomycetes. D-tagatose incubation inhibits β-glucosidase, fructokinase, and phosphomannose isomerase activity, affects sugar content, leading to glycolysis inhibition, tricarboxylic acid (TCA) cycle inhibition, and cell wall biogenesis deficiency. In addition, D-tagatose causes severe mitochondrial alterations, with the consequent decrease in ATP content, reduction in oxygen consumption rate (OCR), accumulation of reactive oxygen species (ROS), increase of oxidative stress, and downregulation of gene expression. Increases (green arrow) or decreases (red arrow) in metabolic processes and intermediates are visualized according to D-tagatose effects on phytopathogenic oomycetes (Chahed et al., 2020, 2021; Corneo et al., 2021b; Mochizuki et al., 2020) using Servier Medical Art templates (https://smart.servier.com) [Colour figure can be viewed at wileyonlinelibrary.com]

with a partial uncoupling of respiration and oxidative phosphorylation processes (Crocken & Tatum, 1968). Mitochondrial alterations in *P. infestans* incubated with D-tagatose could be associated with a dysfunction of ATP synthase activity, as found in yeast cells (Gavin et al., 2004; Paumard et al., 2002; Weimann et al., 2008), and with a decreased mitochondrial bioenergetic status and ATP content, as found in human subjects exposed to D-tagatose (Buemann et al., 2000). Likewise, chemical fungicides negatively affect respiration processes and energy generation systems in *Phytophthora* spp., such as cyazofamid (Mitani et al., 2001) and fomoxadone (Jordan et al., 1999) in *P. infestans*, SYP 14288 (Wang et al., 2018) and pyrimorph (Yan et al., 2010) in *P. capsici*, with impacts on mitochondrial cristae (e.g., oxadixyl and metalaxyl in *P. infestans* and *P. megasperma* var. *sojae*, respectively; Jiang & Grossmann, 1991; Stossel, 1982).

The alterations of mitochondrial processes found in *P. infestans* incubated with D-tagatose (Chahed et al., 2020) are associated with sugar metabolism inhibition (Chahed et al., 2021; Corneo et al., 2021b; Mochizuki et al., 2020). In particular, *H. arabidopsidis* growth inhibition caused by D-tagatose is ascribed to a competitive inhibition of fructokinase and phosphomannose isomerase enzymes (Mochizuki et al., 2020). Because fructokinase can phosphorylate both D-fructose and D-tagatose, the incubation of *H. arabidopsidis* with D-tagatose decreases D-fructose 6-phosphate content and increases D-tagatose 6-phosphate content (Mochizuki et al., 2020). Consequently, D-tagatose 6-phosphate inhibits phosphomannose isomerase and leads to a decrease in D-mannose 6-phosphate and D-glucose 6-phosphate production (Mochizuki et al., 2020). The cell wall of oomycetes is mainly composed of D-glucose and D-mannose polymers (Melida et al., 2013) and phosphomannose isomerase inhibition may be responsible for cell wall biogenesis deficiency and growth inhibition (Mochizuki et al., 2020). Likewise, L-sorbose alters *N. crassa* cell wall and reduces the content of substrates for cell wall synthesis (Crocken & Tatum, 1968), suggesting common effects of rare sugars on the microbial cell wall.

D-tagatose is known as a glycolysis inhibitor in human cells (Kim et al., 2014) and shows inhibitory effects on fructose phosphate aldolase in *E. coli* (Stellmacher et al., 2016), and fructokinase (Lu et al., 2008) and glucosidase (Espinosa & Fogelfeld, 2010) in mammals. In *P. infestans*, D-tagatose decreases β-glucosidase activity and D-glucose, D-glucose 1-phosphate, and D-mannose content, while it increases D-fructose, D-galactose, and D-sucrose content (Corneo et al., 2021b). Accordingly, D-tagatose impairs the sugar and amino acid metabolism with the downregulation of genes involved in sugar metabolism, sugar transport, signal transduction,

and growth-related processes in *P. infestans* (Chahed et al., 2021). As a possible consequence of glycolysis inhibition, the content of tricarboxylic acid cycle intermediates (e.g., malic acid, succinic acid, and α-ketoglutaric acid; Corneo et al., 2021b) and the expression of genes implicated in the tricarboxylic acid cycle (e.g., malate synthase, succinate-semialdehyde dehydrogenase, succinate dehydrogenase, and pyruvate dehydrogenase; Chahed et al., 2021) are decreased by D-tagatose incubation in *P. infestans*. Similarly, the mode of action of some chemical fungicides are based on the inhibition of key metabolic process in *Phytophthora* spp., such as mandipropamid on cell wall biosynthesis in *P. infestans* (Blum et al., 2010) and pyrimorph on glycolysis, tricarboxylic acid cycle, hexose monophosphate and cell wall biosynthetic pathways in *P. capsici* (Pang et al., 2015; Yan et al., 2010). Inhibitory effects on microbial enzymes can also be caused by other rare sugars, such as L-sorbose 1-phosphate and L-sorbose 1,6-bisphosphate on yeast aldolase (Richards & Rutter, 1961), D-xylitol on *S. mutants* phosphofructokinase (Assev & Rolla, 1986), and the sugar analogue 2-deoxy-D-glucose on yeast phosphohexose isomerase and glucose 6-phosphate dehydrogenase (Moore, 1981). The existence of antagonistic interactions between rare sugars and common sugar metabolism is suggested by the attenuation of D-tagatose effects in *P. infestans* (Corneo et al., 2021b) and *S. mutants* (Hasibul et al., 2018) growth in the presence of D-fructose, but not D-glucose. In particular, D-tagatose-mediated growth inhibition and metabolite changes can be fully impaired by the presence of D-fructose, while they are only partially attenuated by the presence of D-glucose, and not influenced by the presence of D-sucrose in *P. infestans* (Corneo et al., 2021b). Likewise, *Caenorhabditis elegans* growth inhibition by D-arabinose incubation is recovered by D-fructose, but not D-glucose, suggesting that D-arabinose interferes with D-fructose metabolism (Sakoguchi et al., 2016). The root growth inhibition of *Arabidopsis thaliana* seedlings by D-allose is prevented by D-glucose (Kato-Noguchi et al., 2011), indicating antagonistic interactions between rare sugars and the metabolism of their respective epimers.

Thanks to their similar chemical structure, D-tagatose and D-fructose can serve as substrates for the same enzymes and lead to competition for catalytic sites (Mochizuki et al., 2020). Previous studies showed that the hydroxyl group of the third carbon (C3-OH group) is implicated in the binding of D-fructose to fructose-metabolizing enzymes (Bertrand et al., 1998; Nocek et al., 2011) and in the correct orientation of glucosidase inhibitors (e.g., flavonoids) in the binding pocket of the target enzyme (Xu, 2010). Among all the rare sugars tested (Figure 1), those with a similar C3 spatial configuration of D-fructose and with a different configuration of the fourth and fifth carbon inhibit *P. infestans* growth (i.e., D-tagatose and L-sorbose), while those with a different C3 spatial configuration do not (i.e., D-psicose and D-sorbose). Similarly, Kobayashi et al., (2010) confirmed the importance of α-axial hydroxyl group at the C3 position of D-allose for the retarding activity on rice seedling growth. Thus, structural configurations of rare sugars may be responsible for competitive inhibition of key enzymes of the sugar metabolism, but further biochemical studies are required to verify interactions of rare sugars with sugar transporters and catalytic sites of metabolic enzymes.

Although D-tagatose inhibits *P. infestans* and *H. arabidopsidis* metabolism and growth (Chahed et al., 2020; Corneo et al., 2021b; Mochizuki et al., 2020), species-specific effects are observed in *Phytophthora* spp. (Chahed et al., 2020, 2021). In particular, *Phytophthora cinnamomi* growth and mitochondrial ultrastructure are only slightly affected by D-tagatose with no impacts on ATP content, respiration processes, ROS accumulation, sugar content, and amino acid content (Chahed et al., 2020, 2021). *P. cinnamomi* response to D-tagatose includes an efficient upregulation of genes involved in glucose transport, pentose metabolism, tricarboxylic acid cycle, reactive oxygen species detoxification, mitochondrial respiration, and alternative respiration that possibly attenuate the negative impacts of the rare sugar (Chahed et al., 2021). Species-specific effects of D-tagatose are known also in the *Trichoderma* genus, where D-tagatose supported the growth of *T. harzianum* and *T. pleuroticola*, but not that of *T. pleurotum* (Komon-Zelazowska et al., 2007). Likewise in the *Lactobacillus* genus, D-tagatose can be assimilated by *L. plantarum*, *L. acidophilus*, and *L. brevis*, but not by *L. buchneri* (Bautista et al., 2000), indicating possible selective effects of this rare sugar. Selectivity of a fungicide is considered as a positive trait, due to the limited side effects on other microorganisms, but further functional studies are required to verify the differential inhibitory activities of D-tagatose on a large spectrum of plant-associated microbial taxa. Moreover, the species-specific effects of D-tagatose in *Phytophthora* spp. raise the question of whether species inhibited by this rare sugar can further acquire resistance traits and evolve metabolic adaptations. Further enzymatic and biochemical studies are needed to clarify the differential inhibitory mechanisms of D-tagatose in *Phytophthora* spp. Functional genomic approaches would be interesting, in order to verify whether *P. cinnamomi* genes can increase tolerance to this rare sugar once introduced in *P. infestans*. Moreover, the growth inhibition of *P. infestans* is reversible and mycelial growth can be restored on a D-tagatose-free growth medium (Chahed et al., 2020), suggesting that efficacy trials of formulated products are needed in order to better verify the stability and persistence of D-tagatose under field conditions.

4 | D-TAGATOSE DOES NOT SEEM TO ACT AS A PLANT RESISTANCE INDUCER

D-tagatose does not seem to act as a plant resistance inducer (Mochizuki et al., 2020) unlike other rare sugars, such as D-psicose and D-allose (Kano et al., 2011). In particular, D-tagatose does not modulate the expression of defence-related genes in cucumber, rice, and *A. thaliana* (Mochizuki et al., 2020). For example, the transcriptome analysis of *A. thaliana* does not show any significant modulation of hormone- and defence-related genes (e.g., pathogenesis-related proteins, peroxidase, lipoxygenase, and pore-forming toxin-like protein) in response to D-tagatose treatment and *H. arabidopsidis* inoculation (Mochizuki et al., 2020). Thus, downy mildew suppression by

D-tagatose is mainly related to direct inhibition of *H. arabidopsidis* growth rather than induction of *A. thaliana* resistance (Mochizuki et al., 2020). Conversely, D-psicose and D-allose upregulate the expression of defence-related genes (e.g., lipoxygenase L-2, β-1,3-glucanase, peroxidase, and chitinase) in rice, resulting in enhanced plant resistance against *Xanthomonas oryzae* (Kano et al., 2011). Therefore, slight structural differences of rare sugars may strongly affect their functional properties, indicating that further functional and molecular studies are required to clarify the effect of rare sugars on plant resistance induction. For example, D-psicose induces rice resistance against *X. oryzae* (Kano et al., 2011), but it does not inhibit *P. infestans* growth (Chahed et al., 2020), while D-tagatose does not induce rice resistance (Mochizuki et al., 2020), but inhibits *P. infestans* growth (Chahed et al., 2020). Thus, the combination of D-tagatose with D-psicose in crop protection strategies could complement their effects on direct inhibition of phytopathogen growth and plant resistance activation. However, possible side effects of rare sugars on plant growth and crop yield or quality cannot be totally excluded and effects of D-tagatose should be further evaluated in different crops under field conditions. For example, rice root and shoot growth are inhibited by D-allose, but not by D-altrose and D-sorbose, (Kano et al., 2010) through a hexokinase-dependent pathway (Fukumoto et al., 2013). Likewise, D-psicose inhibits lettuce (Kato-Noguchi et al., 2005) and *A. thaliana* (Kato-Noguchi et al., 2011) growth, while it can increase the sugar content and reduce the incidence of blossom end rot in tomato fruits (Yamada et al., 2014).

5 | CONCLUSION

D-tagatose inhibits the growth of phytopathogenic oomycetes and has been proposed as a promising plant protection product with no negative effects on human health and the environment. Studies performed so far showed that the mode of action of D-tagatose against phytopathogenic oomycetes is mainly based on the inhibition of sugar metabolism and mitochondrial processes. The growth inhibition of phytopathogenic oomycetes can be ascribed to structural similarities of D-tagatose with D-fructose and to competitive inhibition of key metabolic enzymes. The multiple mechanisms of action of D-tagatose against *P. infestans* suggest that it would probably be difficult for phytopathogenic oomycetes to develop resistance strategies against this rare sugar. However, D-tagatose species-specific effects in *Phytophthora* spp. and its possible nutritional properties on some beneficial plant-associated microorganisms needs further investigations. Although the specificity of plant protection products may be associated with low side effects on nontarget microorganisms, further functional studies are required to understand the differential mechanisms of D-tagatose on a large spectrum of phytopathogenic taxa and to identify transporters and enzymes responsible for *P. cinnamomi* tolerance to this rare sugar.

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CONFLICT OF INTEREST

A. C. and A. N. were employed by Bi-PA nv. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in the study.

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