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Potential of T3SS Inhibitors for Bacterial Plant Disease Management

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SUMMARY

Traditional methods for managing plant bacterial diseases, such as antibiotics and copper preparations, come with significant drawbacks as growing concern of antibiotic resistance and accumulation of copper-based bactericides in the environment. A promising alternative approach focuses on virulence factors rather than bacterial growth, like targeting the type III secretion system (T3SS), a well-conserved mechanism in gram negative bacteria. Researchers have identified both natural and synthetic small-molecule inhibitors of the T3SS that have shown efficacy against various bacterial pathogens and diseases.

INTRODUCTION

Presently, the predominant methods for managing plant bacterial diseases involve the use of copper preparations and agricultural antibiotics. However, these approaches come with unintended consequences. Copper preparations, for instance, have the potential to accumulate in the environment, leading to environmental contamination. Simultaneously, the agricultural industry grapples with the escalating issue of antibiotic resistance. Traditional antibiotics, designed to target the growth and survival mechanisms of pathogens, exert significant selection pressures on pathogenic bacteria, fostering the development of antibiotic resistance (D'Costa *et al*., 2011). A promising alternative to address pathogen resistance involves focusing on virulence factors without impacting bacterial growth (Rasko and Sperandio, 2010; Feng *et al*., 2019). The innovative future methods of disease management focus on more specific and strategic approach, for example through targeting the pathogen virulence. The Anti-virulence agent modulating pathogenesis related to process such as biofilm formation, quorum sensing (QS) and type III secretion system (T3SS) is currently being explored as a new strategy to manage bacterial diseases.

Type III secretion system

The type III secretion system (T3SS) injects bacterial effector proteins into host cells to suppress their defences. It is a highly conserved virulence factor in many Gram-negative pathogenic bacteria and this is not necessary for bacterial survival *in vitro*. Thus, it is regarded as an ideal target for the development of novel antimicrobial drugs (Charro and Mota, 2015).

Type III secretion system inhibitors

T3SS inhibitors are referred to as small molecules that could specifically inhibit the synthesis or functionality of the T3SS. It inhibits the activity of T3SS, blocking effectors from entering host cells through autonomous or passive immune pathways and preventing pathogens from infecting host cells. This mechanism of action of T3SS inhibitors is different from conventional antibiotics because they only target the virulence rather than the viability of bacteria, thus reducing the selection pressure of bacteria and the possibility of drug resistance. Many researchers have reported these inhibitors either from natural origin and synthetic compounds with T3SS inhibition property with known mode of action which suppresses the growth of different plant pathogenic bacteria are described below (Table 1 and 2).

Table 1: Natural compounds with T3SS inhibition activity

	T3SS inhibitors	Mode of action	Pathogens
1	p-coumaric acid (PCA)	represses the expression of T3SS regulatory genes through the HrpX/Y two-component system	*Dickeya dadantii*
2	o-coumaric acid (OCA)	affect the RsmB–RsmA pathway and induce the expression of the T3SS gene *hrpA*	*Xanthmonas oryzae* pv. *oryzae* and *Dickeya dadantii*

3	trans-4-hydroxycinnamohydroxamic acid (TS103)	through a reduction in the RNA levels of the regulatory small RNA RsmB, post-transcriptional level- inhibits hrpL	*Dickeya dadantii*
4	trans-4 phenylcinnamic acid	affect the CsrB, a global regulatory small RNA, at the posttranscriptional level	*Erwinia amylovora*
5	2-methoxybenzene propanoic acid 3-(2-fluorophenyl)-2-propenoic acid 3-[2-(acetyloxy)phenyl]-2- propenoic acid	mRNA levels of representative genes in the hrp (hypersensitive response and pathogenicity) cluster, as well as the regulatory genes hrpG and hrpX, were reduced.	*Xanthmonas oryzae* pv. *oryzae*
6	4-hydroxybenzoic acid and vanillic acid	2.5 mM significantly suppressed the expression of hopP1, hrpA, and hrpL in the hrp/hrc	*Pseudomonas syringae* pv. *tomato*
7	hopeaphenol,isohopeaphenol and ampelopsin A (resveratrol oligomers)	reduced the transcription levels of the hrpA, hrpL	*Pseudomonas syringae* pv. *tomato*

Table 2: Synthetic compounds with T3SS inhibition activity

	T3SS inhibitors	Mode of action	Pathogens
1	Salicylidene acylhydrazide (SAH)	Represses the promoter activity of hrpN, dspE, hrpL, and hrpA in *Erwinia amylovora* and inhibits T3SS effector translocation.	*Erwinia amylovora*, *Ralstonia solanacearum*
2	Benzyloxy carbonimidoyl dicyanide derivatives	Blocked the secretion of the T3SS effector protein	*Acidovorax citrulli*
3	Benzo-thiazoles, Benzoxazoles and Benzimidazoles	Reduces hrp/hrc gene expression through the HrpR/S-HrpL pathway.	*Pseudomonas syringae*
4	Ethyl 2-nitro-3- arylacrylates	Decrease in mRNA levels of representative genes in the hrp cluster, including the key regulatory genes hrpG and hrpX	*Xanthmonas oryzae pv. oryzae*
5	1,2, 4-triazole and 1,3, 4-oxadiazole compounds	Down-regulated the expression of the T3SS and transcription activator-like effector correlative proteins of *Xoo*	*Xanthmonas oryzae pv. oryzae*
6	1,3-thiazolidine- 2-thione derivatives (Series 2) involving the 5- phenyl-2-furan moiety based on Series 1	Reduce mRNA levels of representative genes in the hrp group with the regulatory genes hrpG and hrpX	*Xanthmonas oryzae pv. oryzae*
7	1,3,4-thiadiazole derivatives	Reduces hrpG and hrpX mRNA levels	*Xanthmonas oryzae pv. oryzae*
8	S-Thiazol-2-yl- furan-2-carbothioate Derivatives	Targets the promoter with a PIP-box	*Xanthmonas oryzae pv. oryzae*
9	cinnamic acid derivatives	Targets HrpG-HrpX regulatory cascade	*Xanthmonas oryzae pv. oryzae*
10	Ethyl-3-Aryl-2- Nitroacrylate Derivatives	Promoters carrying a PIP-box may be the key targets of these inhibitors	*Xanthmonas oryzae pv. oryzae*

CONCLUSION

The innovation of novel molecules that specialized in targeting the primary virulence factor (like T3SS), with least lethal selective pressure on pathogens serve as an alternate bacterial management strategy. The synthesized and naturally occurring chemicals (Several small molecules) have been found to exhibit T3SS inhibitory activities in recent years. The inhibitory mechanisms against small-molecule inhibitors are insufficient, because of complex process of T3SS regulation and an inhibitor that works on the T3SS of one pathogen is likely to fail in another pathogen. The major focus of future studies should be on the mechanisms of newly discovered virulence inhibitors and a successful implementation in the field conditions.

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