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Application of inhibitors targeting the type III secretion system in phytopathogenic bacteria

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ABSTRACT

Plant bacterial diseases have inflicted substantial economic losses in global crop, fruit, and vegetable production. The conventional methods for managing these diseases typically rely on the application of antibiotics. However, these antibiotics often target the growth factors of the pathogenic bacteria, leading to the accumulation and emergence of drug-resistant strains, which exacerbates antibiotic resistance. Innovative methods are urgently needed to treat and prevent the toxicity caused by these pathogenic bacteria. Targeting virulence mechanisms in pathogens is a globally recognized and effective strategy for mitigating bacterial resistance. Type III secretion system (T3SS) serves as a crucial virulence determinant in Gram-negative pathogens, and its non-essentials for pathogen growth renders it an ideal target. Targeting the T3SS holds significant potential to alleviate selective pressure for resistance mutations in pathogens. Therefore, targeting T3SS in pathogenic bacteria, while preserving their growth, has emerged as a novel avenue for the development of antimicrobial drugs. In recent years, a multitude of small molecular inhibitors targeting T3SS have been identified. This article offers a comprehensive review of T3SS inhibitors in plant pathogens, while also presenting the latest research advancements in this research direction.

1. Introduction

Plant diseases present a formidable challenge to agricultural production [1-3]. In recent years, exacerbated by global climate change and alterations in cropping patterns, the frequency and severity of bacterial plant diseases have been steadily rising, leading to escalated damage [4,5]. Approximately 300 out of the known 1600 pathogenic bacteria species are responsible for causing plant bacterial diseases, and there are over 500 known types of plant bacterial diseases. Bacterial diseases such as bacterial wilt, rice bacterial leaf blight, soft rot, and bacterial canker are highly important worldwide [6-10]. Bacterial diseases are ubiquitous and can cause extensive damage, rendering their prevention and control extremely challenging. Once a field is infected, it may become a permanent disease zone, resulting in substantial crop and economic plant losses [11-14]. Currently, agricultural bactericides represent the most efficacious method for disease prevention in agriculture [14-16]. Nevertheless, the available range of bactericides for controlling plant pathogenic bacteria is limited. Furthermore, the rapid reproduction, large population, and mutational capacity of bacteria contribute to the emergence of serious antibiotic resistance issues with frequent application of bactericides [14,17,18].

Traditional bactericides target key bacterial growth factors to suppress or kill them, which can lead to the emergence and accumulation of antibiotic-resistant mutant pathogenic strains, thereby contributing to the development of antibiotic resistance [19-23]. Therefore, exploring new targets and developing novel antibacterial drugs is a crucial aspect in the development of new pesticides [23-27]. Targeting pathogenic bacterial virulence factors without com-

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promising their survival presents a novel approach to the advancement of new antibacterial medications [28-32].

Type III secretion system (T3SS), a highly conserved key virulence factor in Gram-negative pathogenic bacteria, is nevertheless non-essentials for bacterial growth, which renders the T3SS an ideal target for the development of new antibacterial drugs [33-35]. Based on previous research, this article introduces the overview of the T3SS and provides a summary of the T3SS inhibitors identified in recent years, including both natural and synthetic T3SS inhibitors, which offers new insights for the development of novel, efficient, and safe chemical substitutes and serves as a reference for the development of new antibacterial drugs.

2. Research progress

2.1. The structure and regulation of T3SS

The T3SS of pathogenic bacteria is composed of more than 20 proteins that form a needle-like complex with highly conserved structural and functional features [36,37]. T3SS is widely present in Gram-negative pathogenic bacteria, including *Pseudomonas syringae*, *Pseudomonas aeruginosa*, *Erwinia amylovora*, *Ralstonia solanacearum*, *Xanthomonas campestris*, and *Salmonella enterica* [38-42]. It consists of several essential components, including the ATPase complex, the C-ring, the inner membrane export apparatus, the basal body, the needle filament or pilus, the tip complex, and the translocation pore. Together, these components form a transmembrane channel that extends across the inner membrane, outer membrane, and host cell membrane of the pathogenic bacteria [43-45].

The proteins secreted by the T3SS can be classified into four groups: structural component proteins, translocator proteins, effector proteins, and T3SS chaperone proteins [39,46]. The core component of T3SS is the needle-like complex, referred to as the *hrp* pilus in plant pathogenic bacteria. The *hrp* pilus was initially discovered in *S. typhimurium* and subsequently found in other pathogenic bacteria, exhibiting significant conservation in structure and function [47,48]. The *hrp* pilus is essential for the secretion of T3SS effector proteins and is encoded by the *hrpA* in *P. syringae* [49], while it is encoded by the *hrpE* in *Xanthomonas* [50]. All Hrp (hypersensitive response and pathogenicity) and Hrc (hypersensitive response and conserved) proteins are required to form the complete *hrp* pilus [49,51].

T3SS in Gram-negative pathogens is encoded by the *hrp* and *hrc* genes [52,53]. The *hrp/hrc* gene cluster, which encodes the T3SS, is highly conserved and determines the pathogenicity of the pathogen in host plants as well as the hypersensitive response (HR) in non-host plants [52,54]. The *hrp* genes were initially reported in *P. syringae* pv. *phaseolicola* in 1986 and have subsequently been identified in various other plant pathogens, including *X. campestris*, *Pseudomonas syringae*, *Erwinia amylovora*, and *Ralstonia solanacearum* [55,56]. The T3SS is closely linked to pathogenicity in bacterial pathogens. Utilizing its needle-like complex, it infiltrates the host cell membrane and releases substantial quantities of effector proteins into the host cell, which suppress the host immunity while simultaneously facilitating the survival and proliferation of the pathogen (Fig. 1) [57-59].

The *hrp* gene clusters in plant pathogenic bacteria can be divided into two groups: group I and group II. The *hrp* group I includes *P. syringae* and *E. amylovora*, among which the expression of the T3SS in *P. syringae* is primarily regulated by the HrpR/S-HrpL pathway [53,60]. In this pathway, the majority of the downstream genes of T3SS are regulated by the HrpL protein, which belongs to the extracytoplasmic function (ECF) family [61]. HrpL activates the expression of *hrp* genes by binding to the *hrp*-box ($CGAACCNAN_{14}CCACNNA$) in the promoter region of the downstream *hrp/hrc* genes [62-64]. The *hrp* group II includes *R. solanacearum* and *Xanthomonas* spp. [65], Among them, *Xanthomonas* primarily regulates the expression of *hrp* genes through the HrpG-HrpX regulatory pathway. HrpG, belonging to the OmpR family of two-component systems, plays a crucial role in positively regulating the expression of *hrpX* [66]. HrpX, a member of the AraC family, binds to the PIP-box motif ($TTCGB\text{-}N_{15}\text{-}TTCGB$; B: C, G, or T) within the *hrp/hrc* gene promoter and facilitates the transcription of most downstream T3SS genes [67,68].

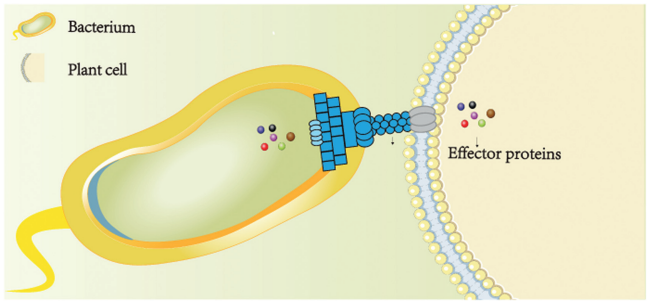


Fig. 1. Pathogenic bacteria utilize T3SS to deliver virulence proteins into host plant cells. Reproduced with permission [59]. Copyright 2023, Wiley (slightly modified).

2.2. Research progress of T3SS inhibitors

In recent years, with the increasing threat of bacterial resistance to agriculture and human health [69-71], the screening of novel antibacterial drugs targeting pathogenic bacterial virulence factors has become a significant research focus [72-76]. T3SS is a highly conserved and critical virulence factor in plant pathogenic bacteria that has attracted considerable attention from researchers [77-79]. There have been a significant number of reports on the screening of T3SS inhibitors, which target various pathogenic bacteria as potential novel antibacterial drugs [80], these inhibitors are predominantly sourced from natural products and chemical synthesis. A considerable amount of research has been reported on the utilization of natural products as inhibitors of T3SS in plant pathogens. However, natural products often necessitate artificial structural modifications for widespread application due to factors such as complex structures and limited stability. In contrast, small molecule compounds synthesized artificially exhibit a relatively simple and readily accessible advantage [81-84]. Nevertheless, the broader utilization of synthetic compounds is often hindered by challenges such as insufficient solubility and significant cytotoxicity. To date, researchers worldwide have devised various screening systems and reporter genes to identify T3SS inhibitors. These reporter systems include luciferase (Lux) reporter systems, green fluorescent protein (GFP) reporter systems, β-glucuronidase (GUS) reporter systems, and phospholipase reporter systems [85-87]. The reported T3SS inhibitors primarily consist of cinnamic acid derivatives, heterocyclic derivatives, pyridine carboxamide derivatives, and carboxylic acid compounds, among others.

2.2.1. Dickeya spp.

In the process of plant-microbe interaction, plants generate a range of defense responses or substances to combat pathogen invasion, including various secondary metabolites. Phenolic compounds are a significant category of organic intermediates synthesized through the secondary metabolism of plants. In 2008, Yang *et al.* discovered that plant phenolic compounds, such as *o*-coumaric acid (OCA, Fig. 2) and *trans*-cinnamic acid (TCA, Fig. 2), demonstrate noteworthy induction activity on the *hrpN* gene promoter of *D. dadantii* 3937 without affecting bacterial growth. The quantitative fluorescence-based reverse transcription polymerase chain

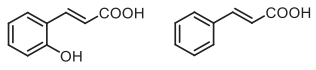


Fig. 2. The structures of compounds OCA and TCA.

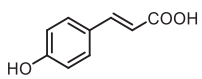


Fig. 3. The structure of compound PCA.

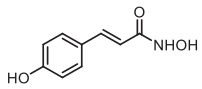


Fig. 4. The structure of compound **TS103**.

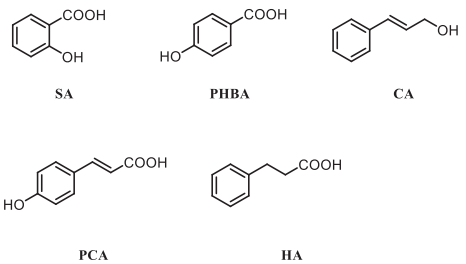


Fig. 5. The structures of five compounds.

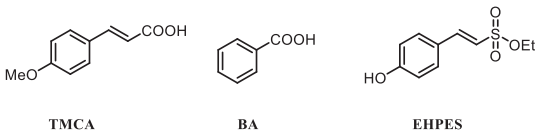


Fig. 6. The structure of TMCA, BA, and EHPES.

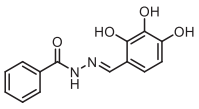


Fig. 7. The structure of compound **3**.

reaction (RT-qPCR) results reveal that OCA and TCA induce the expression of T3SS genes, such as *dspE* (encoding T3SS effector protein), *hrpA* (encoding T3SS *hrp* pilus protein), and *hrpN* (encoding T3SS harpin protein) *in vitro*. This study has revealed the mechanism by which the induction of T3SS expression by OCA and TCA is regulated through the *rsmB*-RsmA pathway. This is the first report of plant phenolic compounds stimulating the expression of T3SS genes in plant pathogenic bacteria [88].

Subsequently, Li *et al.* conducted further research on plant phenolic compounds and their analogs in 2009. They discovered that *p*-coumaric acid (PCA, Fig. 3) exhibited a potent inhibitory effect on the *hrpA* promoter without compromising bacterial growth. The RT-qPCR results demonstrated that PCA inhibited the transcription levels of *dspE*, *hrpL*, *hrpN*, and *hrpS* at a concentration of 100 μmol/L. Further investigation revealed that PCA inhibited T3SS expression primarily through the HrpX/Y-HrpS-HrpL pathway, which is the first reported T3SS inhibitor in plant pathogenic bacteria [87].

In 2015, Li *et al.* screened a range of derivatives of plant phenolic compounds and identified that *trans*-4-hydroxycinnamohydroxamic acid (**TS103**, Fig. 4) exhibited an 8-fold greater inhibitory potency on T3SS in comparison to PCA. Through a comprehensive series of studies, it was determined that **TS103** exerts its inhibitory effect on T3SS by suppressing *hrpY* phosphorylation, leading to a decrease in the levels of *hrpS* and *hrpL* transcripts, ultimately resulting in the suppression of T3SS expression. Furthermore, **TS103** inhibits *hrpL* at the post-transcriptional level by decreasing the RNA levels of the regulatory small RNA RsmB through the *rsmB*-RsmA regulatory pathway [89]. This discovery is the first instance of an inhibitor that effectively inhibits T3SS *via* both transcriptional and post-transcriptional pathways in the phytopathogenic bacteria *D. dadantii* 3937.

In 2022, Hu *et al.* utilized a reporter system constructing *D. zeae hrpA*-GFP to screen for T3SS inhibitors. They identified five compounds that significantly inhibited *hrpA* promoter activity without affecting bacterial growth, including salicylic acid (SA), *p*-hydroxybenzoic acid (PHBA), cinnamic alcohol (CA), PCA, and hydrocinnamic acid (HA) (Fig. 5). All the five compounds exhibited a reduction in the HR in non-host tobacco plants and decreased the transcription of the T3SS regulatory gene *hrpL* and downstream *hrp* genes. Inoculation experiments demonstrated that these five compounds exhibited significant inhibitory effects on the pathogenicity of *D. dadantii* 3937 on potato, *D. fangzhongdai* CL3 on taro, *D. oryzae* EC1 on rice, and *D. zeae* MS2 on banana seedlings [90]. These findings provide potential inhibitors for preventing soft rot disease caused by *Dickeya* spp.

2.2.2. Erwinia amylovora

In 2013, Khokhani *et al.* established an *E. amylovora hrpA*-GFP reporter system and employed flow cytometry to screen for phenolic compounds derived from plants. It was discovered that numerous plant phenolic compounds demonstrate inhibitory or inducible activities against *E. amylovora* T3SS. Among these, compounds TMCA, BA, and EHPES were selected for further investigation (Fig. 6). Preliminary mechanistic studies indicate that two T3SS inhibitors (TMCA and BA) and the T3SS inducer EHPES modulate the expression of T3SS through the HrpS-HrpL pathway. Furthermore, the inhibitor TMCA was found to also suppress the expression of the T3SS system through the *rsmB*-RsmA pathway. In total, plant phenolic compounds have been confirmed to play a significant role in the regulation of T3SS [91].

In 2014, Yang *et al.* found that salicylidene acylhydrazides compounds displayed inhibition on the gene promoter activity of *hrpN*, *dspE*, *hrpA*, and *hrpL* in *E. amylovora*. Specifically, the representative compound **3** (Fig. 7) effectively suppressed the expression of numerous T3SS genes, including the *hrpL* and *avrRpt2* genes, in *E. amylovora*. Simultaneously, compound **3** also hindered the production of amylovoran, an exopolysaccharide (EPS) essential for biofilm formation. Ultimately, the author opted for crab apple flowers for the inoculation experiment, revealing that compound **3** notably mitigated disease progression in pistils [92].

In 2023, Yuan *et al.* selected **TS108** (Fig. 8), a plant phenolic derivative, as the focus of their study to investigate its mechanism of action, based on the research conducted by Khokhani *et al.* [90]. Subsequent investigations revealed that TS108 exerts a negative regulatory effect on CsrB, a globally regulated small RNA, at the post-transcriptional level, leading to the inhibition of *hrpS* expression. This finding suggests that **TS108** may negatively modulate T3SS gene expression through the CsrB-HrpS-HrpL pathway.

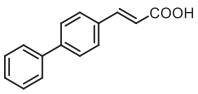


Fig. 8. The structure of compound **TS108**.

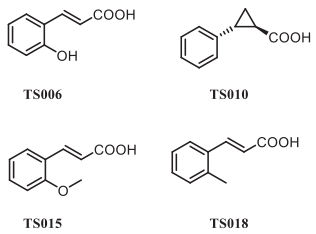


Fig. 9. The structures of **TS006**, **TS010**, **TS015**, and **TS018**.

Additionally, **TS108** had no effect on the expression of T3SS in *D. dadantii* and *P. aeruginosa*, implying a potential specificity of **TS108** inhibition towards *E. amylovora* T3SS. In field trials, the incidence of fire blight was reduced by up to 96.7% following treatment with the **TS108** compared to untreated trees. These results suggest that targeting pathogen virulence factors could offer a promising strategy for controlling fire blight [93]. This study provides further validation for the development and utilization of T3SS inhibitors targeting pathogens.

2.2.3. Xanthomonas *spp.*

In 2017, Fan *et al.* established a GFP reporter system, *hpa1*-GFP, in *X. oryzae* pv. *oryzae* (*Xoo*) and investigated the biological activity of 56 plant-derived phenolic compounds and their derivatives using flow cytometry. They discovered that four compounds, namely **TS006**, **TS010**, **TS015**, and **TS018** (Fig. 9) effectively suppressed the *hpa1* promoter activity without impacting the growth of *Xoo*. The RT-qPCR experiments demonstrated that the transcription levels of *hpa1*, *hrpE*, *hrpF*, *hrcC*, *hrcT*, *hrcU*, and the regulatory genes *hrpG* and *hrpX* were all decreased to varying degrees following treatment with these compounds, which indicates that the compounds effectively suppressed the expression of *Xoo* T3SS *via* the HrpG-HrpX pathway. Through Cya-translocation assays, it was observed that four inhibitors had inhibitory effects on the translocation of two non-TAL effectors (PXO_04172 and PXO_03702) within the T3SS. Furthermore, the influence of these four inhibitors on gum gene expression was examined, and it was found that the mRNA levels of the gum genes remained unchanged, indicating that these inhibitors may not affect the production of EPS. Subsequent inoculation experiments confirmed that the four compounds independently inhibited the pathogenicity of *X. oryzae* pv. *oryzae* (*Xoo*) and *X. oryzae* pv. *oryzicola* (*Xoc*) on rice plants [67]. This study lays a theoretical foundation for the utilization of these four T3SS inhibitors as innovative antibacterial agents combating plant bacterial diseases in agricultural practices.

In 2018, Xiang *et al.* in our group designed and synthesized a set of novel thiazolidin-2-cyanamide derivatives that contain a 5-phenyl-2-furan moiety. These compounds were assayed for activity using the GFP assay system, revealing that **XXWII-2**, **II-3**, and **II-4** (Fig. 10) inhibited the promoter activities of *hpa1*, *hrpG*, and *hrpX* while not impacting the growth of *Xoo*. The RT-qPCR experiments unveiled a significant reduction in the mRNA levels of *hpa1*, *hrpE*, *hrpF*, *hrcC*, *hrcT*, and *hrcU* following treatment with these compounds. Furthermore, these compounds were shown to inhibit the HR of *Xoo* on non-host tobacco plants and the pathogenicity of *Xoo*

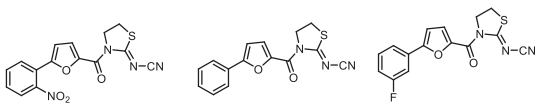


Fig. 10. The structures of compounds **XXWII-2**, **II-3**, and **II-4**.

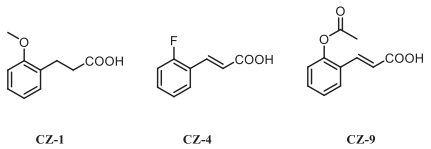


Fig. 11. The structure of compounds **CZ-1**, **CZ-4**, and **CZ-9**.

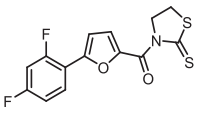


Fig. 12. The structure of compound **III-7**.

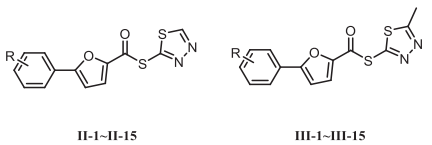


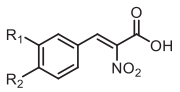
Fig. 13. The structures of compounds **II** and **III**.

on host rice, thereby alleviating the damage caused by rice bacterial leaf blight [94].

Based on previous research highlighting natural products as small molecules with promising bioactivity, in 2019, Tao *et al.* in our group performed activity assays on a selection of natural products utilizing the *hpa1*-GFP reporter system. The three natural product derivatives, **CZ-1**, **CZ-4**, and **CZ-9** (Fig. 11), were identified as inhibitors of *Xoo* T3SS. These compounds exhibited effective preventive and therapeutic effects against both rice bacterial leaf blight and rice bacterial leaf streak disease, providing a theoretical basis for the prevention and control of rice diseases [95].

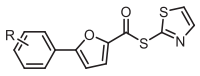
Research by Xiang *et al.* demonstrates that 5-phenyl-2-furan is a small molecule scaffold with favorable biological activity. Based on this, in 2019, Tao *et al.* in our group designed and synthesized a series of 1,3-thiazolidine-2-thione derivatives containing a 5-phenyl-2-furan moiety. Compound **III-7** (Fig. 12) was identified as a potent T3SS inhibitor through a high throughput screening system. The RT-qPCR analysis further confirmed that **III-7** effectively suppressed the transcriptional levels of *Xoo* T3SS. Additionally, compound **III-7** showed remarkable therapeutic efficacy against rice bacterial leaf blight [96]. In the same year, Tao *et al.* designed and synthesized two new series of 1,3,4-thiadiazole derivatives containing 5-phenyl-2-furan (Fig. 13) as potential *Xoo* T3SS inhibitors [97].

In 2019, Jiang *et al.* in our group designed and synthesized a series of cinnamic acid derivatives. Through screening using the *hpa1*-GFP reporter system, they identified three compounds, namely **I-9**, **I-12**, and **I-13** (Fig. 14), which showed potential inhibitory activity against the T3SS of *X. campestris* pv. *campestris* (*Xcc*). It is speculated that these three compounds can potentially decrease the expression of *hrp/hrc* genes *via* the HrpG-HrpX path-



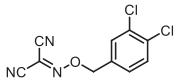
I-9 R_1=OMe R_2=OBn
I-12 R_1=OBn R_2=OMe
I-13 R_1=H R_2=Cyclopentyloxy

Fig. 14. The structures of compounds **I-9**, **I-12**, and **I-13**.



III-1~III-15

Fig. 15. The structures of compounds **JSIII**.



BCD03

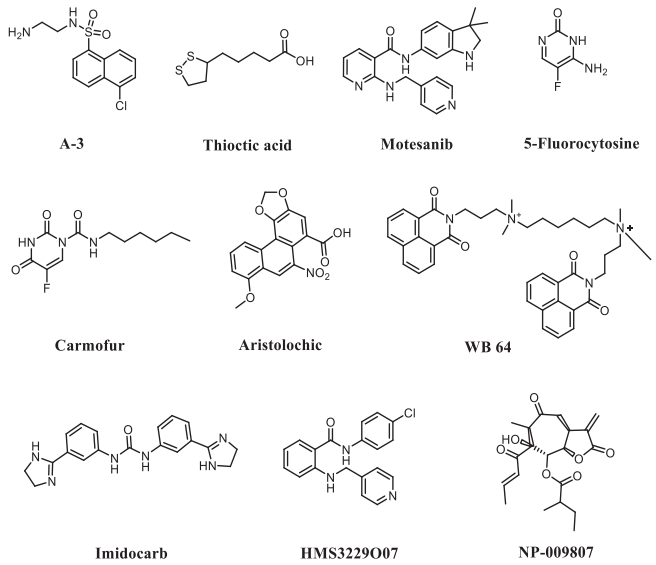
Fig. 16. The structure of compound **BCD03**.

way, thereby diminishing the pathogenicity of *Xcc* on radish and *Xoo* on rice [98].

Based on the research by Xiang *et al.* and Tao *et al.*, in 2019, Jiang *et al.* in our group designed and synthesized a series of *S*–thiazol-2-yl-furan-2-carbothioate derivatives. They evaluated the biological activity of the synthesized compounds using a GFP reporter system. Five compounds, specifically **JSIII-2**, **JSIII-4**, **JSIII-6**, **JSIII-9**, and **JSIII-15** (Fig. 15), demonstrated inhibitory effects on the promoter activities of the *hpa1*, *hrpG*, and *hrpX* genes. Following treatment with these five compounds, there was a notable decrease in the transcription levels of *hrpE*, *hrpF*, *hrcC*, and *hrcU*, suggesting their ability to potentially suppress the expression of the *Xoo* T3SS *via* the HrpG-HrpX pathway. Phenotypic assays unveiled that the compounds specifically targeted the T3SS, as they did not impact the secretion of extracellular cellulases, extracellular xylanases, and exopolysaccharides. Additionally, these compounds reduced the pathogenicity of *Xoo* and *Xoc* on rice, mitigating both rice bacterial leaf blight and rice bacterial streak disease. Thus, these compounds exhibit significant potential for practical applications [99].

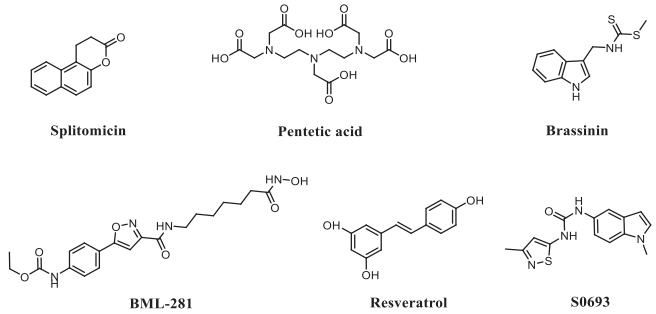
In 2019, Ma *et al.* employed a novel reporter vector that incorporated a fusion of the β-lactamase gene with the signal peptide sequence of a T3SS effector gene to conduct screening for T3SS inhibitors. They observed that the compound **BCD03** (3,4-dichlorobenzyloxy carbonimi-doyl dicyanide, Fig. 16) effectively diminished the HR response of *Xoo* on tobacco at non-bactericidal concentrations. Moreover, the introduction of compound **BCD03** led to a reduction in the secretion of the T3SS effector protein AvrXa27 [100].

In 2020, Zhou *et al.* conducted a screening of a library containing 13,129 small molecule compounds, resulting in the identification of ten compounds that exhibited inhibitory effects on the expression of the T3SS in *Xcc*. Among these compounds, five compounds (**A-3**, carmofur, HMS3229O07, thioctic acid, and **WB 64**) showed remarkable therapeutic effects against *Xcc* virulence in radishes (Fig. 17). By analyzing RT-qPCR, the authors identified that these compounds may exert their inhibitory effects on *hrp/hrc* genes by specifically targeting the regulatory proteins HpaS and sensor kinase proteins ColS. Meanwhile, Zhou *et al.* also identified six compounds (Fig. 18) that effectively induced the *Xcc* T3SS, with pentetic acid being able to induce the HR of *Xcc* on non-host to-



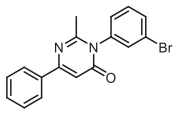
A-3 Thioctic acid Motesanib 5-Fluorocytosine
Carmofur Aristolochic WB 64
Imidocarb HMS3229O07 NP-009807

Fig. 17. The structures of ten compounds inhibiting *Xcc* T3SS.



Splitomicin Pentetic acid Brassinin
BML-281 Resveratrol S0693

Fig. 18. The structures of six compounds inducing *Xcc* T3SS.



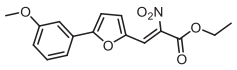
SPF-9

Fig. 19. The structure of compound **SPF-9**.

bacco and enhance pathogenicity on host radishes [101]. In combination, these small molecules have the potential to serve as valuable tool compounds in the ongoing development of antivirulence candidates to control diseases caused by the plant pathogen *Xcc*.

In 2023, Li *et al.* in our group synthesized a series of pyrimidine derivatives and assessed their activity using a Lux reporter system *Xcc*-p*xopN*. The results of the biological activity assays revealed that compound **SPF-9** (Fig. 19) displayed significant T3SS inhibitory activity, effectively reducing the HR in tobacco and suppressing the transcription of certain representative *hrp/hrc* genes. Preliminary mechanistic investigations unveiled that compound **SPF-9** exerted its effects by suppressing the HrpG-HrpX pathway of the *Xcc* T3SS, consequently diminishing the pathogenicity of *Xcc*. As a promising novel T3SS inhibitor with robust anti-*Xcc* activity, compound **SPF-9** exhibits significant potential for future advancements and development [59].

In 2023, Gao *et al.* in our group synthesized a series of novel ethyl-3-aryl-2-nitropropenoate derivatives, among which



B9

Fig. 20. The structure of compound **B9**.

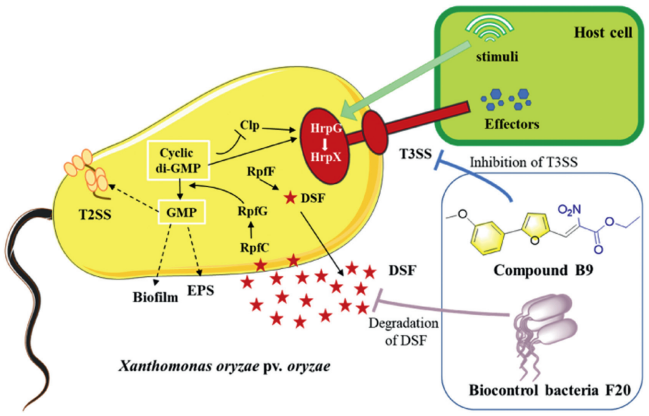


Fig. 21. The working model for controlling *Xoo* pathogenicity in rice through the combination of the T3SS inhibitor **B9** and quorum quenching bacteria F20. Reproduced with permission [102]. Copyright 2023, American Chemical Society.

compound **B9** (Fig. 20) was identified to exhibit enhanced inhibitory activity against *Xoo* T3SS according to the bioassay results. Compound **B9** effectively inhibited the transcription of crucial genes in *Xoo* T3SS, resulting in a significant reduction in the incidence of rice bacterial leaf blight disease. To enhance the efficacy of the drug against the pathogen, the authors utilized a combination of the T3SS inhibitor and the quorum quenching bacteria *Ralstonia pickettii* F20, which resulted in a notable improvement in the control of bacterial leaf blight (Fig. 21) [102]. This study not only introduces a novel approach to prevent and control rice bacterial leaf blight, but also provides a theoretical backing for exploring innovative strategies to control pathogenic bacteria in the future.

In 2023, a series of 1,3,4-thiadiazole thioester derivatives containing 5-phenyl-2-furan were designed and synthesized by Wang *et al.* in our group. Eight inhibitors (**II-2**, **II-3**, **II-5**, **II-6**, **II-10**, **II-12**, **II-13**, and **II-15**, Fig. 13) with excellent protective effects and specific targeting to the *Xanthomonas citri* subsp. *citri* jx-6 (*Xcci* jx-6) T3SS were obtained through inhibitor screening systems, determination of growth curves, tobacco HR, and citrus leaf inoculation. The authors conducted a study on compound **II-15** and performed initial investigations into the mechanism of this inhibitor using RT-qPCR and Western blot. The results showed that the inhibitor effectively decreased the expression of *Xcci* T3SS-related genes and impeded the secretion of effector proteins, thereby reducing the ability of the pathogen to suppress citrus plant immunity, ultimately leading to successful control of citrus canker disease (Fig. 22) [103]. This study is the first to report that 5-phenyl-2-furan derivatives can serve as effective T3SS inhibitors for the control of citrus canker.

The extracts from *Cryptolepis sanguinolenta* (Lindl.) Schlechter, including cryptolepine, neocryptolepine, isocryptolepine, and their derivatives, exhibit excellent antibacterial activity [104,105]. In 2023, Shao *et al.* in our group synthesized a series of cryptolepine and neocryptolepine derivatives and performed bioassays on these compounds. They observed that compound **Z-8** (Fig. 23) selectively targeted the T3SS of *Xoo*, suppressed the transcription of representative TAL and non-TAL effectors, and effectively alleviated the impact of rice bacterial leaf blight disease to some extent. Ultimately, they co-administered the T3SS inhibitor **Z-8** with the quorum quenching bacteria *Ralstonia pickettii* F20 to control rice bacterial leaf blight caused by *Xoo*. The results highlighted a synergistic effect when both were used concurrently, which provided experimental evidence and theoretical support for the development of novel antibacterial agents against pathogenic bacteria [106].

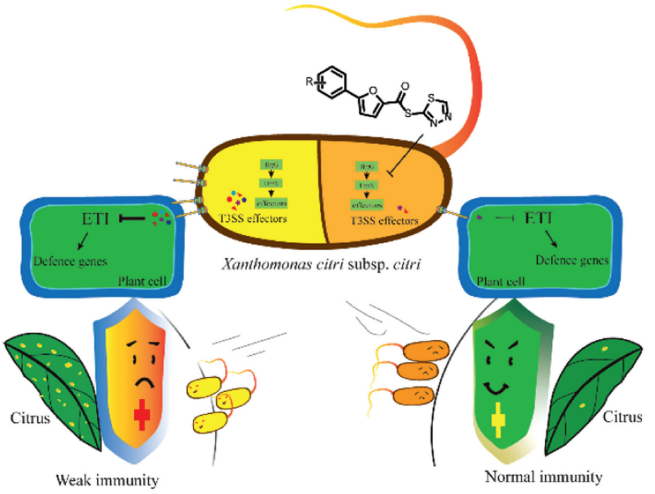
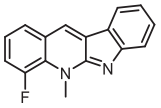
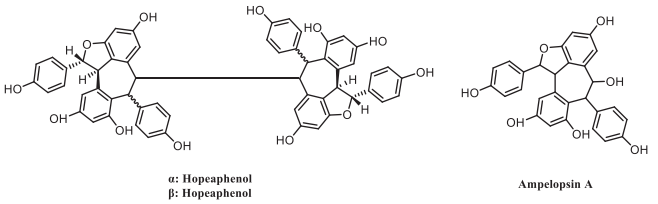


Fig. 22. The mode of action of the T3SS inhibitor **II-15**. Reproduced with permission [103]. Copyright 2023, American Chemical Society.



Z-8

Fig. 23. The structure of compound **Z-8**.



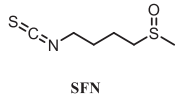
α: Hopeaphenol
β: Hopeaphenol
Ampelopsin A

Fig. 24. The structures of hopeaphenol, isohopeaphenol, and ampelopsin A.

2.2.4. Pseudomonas syringae

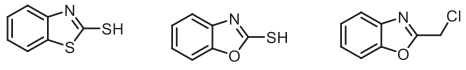
In 2019, Ma *et al.* observed that the compound **BCD03** (Fig. 16) potently reduced the HR response of *P. syringae* pv. *tomato* (*Pst*) on tobacco. In addition, the secretion of the T3SS effector protein AvrPto was markedly reduced after treatment with the compound **BCD03** [100].

In 2020, Kang *et al.* constructed a *Pst hrpA*-GFP reporter strain to screen a plant extract library and found that the root extract of *Vitis vinifera* L. showed remarkable inhibitory activity against the *hrpA* promoter. After isolating and purifying compounds from the root extract, three resveratrol oligomers hopeaphenol, isohopeaphenol, and ampelopsin A (Fig. 24) were identified that notably decreased the transcription levels of *hrpA*, *hrpL*, and *hopP1* genes. Moreover, the three compounds showed inhibitory effects on *Pst* auto-aggregation, indicating that they indeed inhibited the T3SS of *Pst*. Pathogenicity tests showed that the three compounds reduced the virulence of *Pst* in tomatoes [107].



SFN

Fig. 25. The structure of compound SFN.



II-14 II-15 II-24

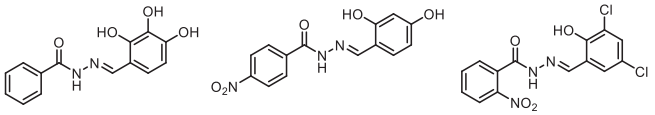
Fig. 26. The structures of compounds **II-14**, **II-15**, and **II-24**.

In 2020, Wang *et al.* made a significant discovery that crude extracts of *Arabidopsis* were capable of substantially inhibiting the expression of the T3SS in *Pst*. Through a series of experiments involving isolation, purification, and structural identification of the crude extracts, the authors successfully identified the active compound responsible for the inhibitory effects as sulforaphane (SFN, Fig. 25), a defense compound naturally found in *Arabidopsis*. They then demonstrated that SFN effectively suppresses the activity of the T3SS in pathogenic bacteria, leading to a reduction in pathogen virulence and ultimately enhancing the plant's resistance to diseases. Additionally, using a chemical proteomic approach, the authors identified HrpS as the specific target protein of SFN. Their study revealed that SFN directly binds to the cysteine at position 209 of the HrpS protein, thereby inhibiting the formation of the HrpS and HrpR hexamer, which leads to the suppression of the T3SS in pathogenic bacteria. Following this biological mechanism, SFN can selectively diminish the pathogenicity of pathogens while avoiding toxicity to beneficial plant microbiota, thereby assuming a targeted defensive function. This study suggests that plants contain secondary metabolites that are capable of reducing the virulence of pathogens without inducing bacterial death. The study clarified the specific mode of action of SFN, which provides a theoretical and scientific foundation for the study of targets and the subsequent application of T3SS inhibitors [108].

In 2023, He *et al.* in our group established a high-throughput screening reporter system based on Lux to screen for T3SS inhibitors, revealing that three heterocyclic compounds (**II-14**, **II-15**, and **II-24**, Fig. 26) significantly inhibited the *hrpW* and *hrpL* gene promoter activities, demonstrating inhibitory activity superior to the positive control SFN. These three compounds may inhibit the expression of T3SS and subsequently reduce the pathogenicity of *Pst* through the HrpR/S-HrpL regulatory pathway, while the representative compound **II-15** markedly inhibited the secretion of the AvrPto effector protein [109].

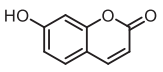
2.2.5. Acidovorax citrulli

In 2019, Ma *et al.* developed a reporter vector, pZAC-3502sig-*penAC*, which fused the β-lactamase gene with the T3SS effector gene *penAC* signal peptide sequences to screen for T3SS inhibitors of *Acidovorax citrulli* (*A. citrulli*). After screening over 12,000 compounds, a series of benzyloxy carbonimidoyl dicyanide (BCDs) derivatives with potent T3SS inhibitory activity were identified, among which compound **BCD03** (Fig. 16) showed a notable decrease in the HR response caused by *A. citrulli*, *Pst*, and *Xoo* on non-host tobacco plants. The inhibitory effect of **BCD03** on the secretion of T3SS effector proteins from the aforementioned bacteria was validated through western blot experiments. In conclusion, the findings indicate that BCD derivatives hold promise as novel T3SS inhibitors against diverse plant pathogenic bacteria, underscoring their potential value for practical applications [100].



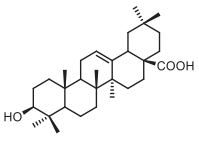
SA1 SA2 SA3

Fig. 27. The structures of compounds **SA1**, **SA2**, and **SA3**.



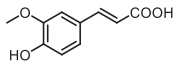
UM

Fig. 28. The structure of compound UM.



OA

Fig. 29. The structure of compound OA.



FA

Fig. 30. The structure of compound FA.

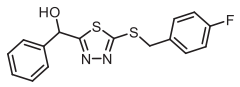
2.2.6. Ralstonia solanacearum

In 2019, Puigvert *et al.* developed a *R. solanacearum PhrpY::luxCDABE* reporter system by fusing the *hrpY* promoter, which encodes the *hrp* pilus, with the *luxCDABE* operon. Through investigations, they discovered that salicylidene acylhydrazides derivatives **SA1**, **SA2**, and **SA3** (Fig. 27) could act as inhibitors of the T3SS in *R. solanacearum*. Inoculation experiments confirmed that the salicylidene acylhydrazide compounds reduced the severity of disease caused by *R. solanacearum*, and protected tomato plants from bacterial speck disease induced by *Pst* [110].

In 2017, Yang *et al.* found that the plant natural product umbelliferone (UM, Fig. 28) greatly inhibited the expression of *R. solanacearum* T3SS by modulating the HrpG-HrpB and PrhG-HrpB pathways, while also suppressing biofilm formation. However, the target and regulatory mechanisms of UM remain unclear [111].

During the research process, the research group from Southwest University discovered natural products that induced the expression of the T3SS in *R. solanacearum*. In 2015, Wu *et al.* found that oleanolic acid (OA, Fig. 29) significantly induced the expression of the T3SS in *R. solanacearum* through the HrpG-HrpB pathway [112]. Furthermore, in 2017, Zhang *et al.* detected that ferulic acid (FA, Fig. 30) induced T3SS expression through the PrhA-prhI/R-PrhJ-HrpG-HrpB signal cascade, highlighting plant-derived compounds as a rich source of regulators for the T3SS in *R. solanacearum* [113].

In 2023, Guo *et al.* in our group conducted a bioactivity evaluation of the designed and synthesized amygdalic acid derivatives. During this evaluation, they found that compound **F-24** (Fig. 31) significantly inhibited the activity of the *hrpY* gene promoter, attenuating the HR and pathogenicity of *R. solanacearum*. Further mechanistic investigations revealed that **F-24** inhibits T3SS through the PhcR-PhcA-PrhG-HrpB pathway, suggesting its great potential as a T3SS inhibitor in *R. solanacearum* [114].



F-24

Fig. 31. The structure of compound **F-24**.

3. Conclusion

In recent years, the increasing threat posed by antibiotic-resistant pathogenic bacteria to agricultural production and human health has propelled the study of novel antibacterial drugs that target the virulence factor T3SS into a prominent research focus. Despite significant progress has been made in identifying various T3SS inhibitors from compound libraries using various screening systems, the targets and mechanisms of most inhibitors remain unknown. In the development of novel pesticides, conducting additional research on the mechanism of action is critical to propel the progress of these innovative inhibitors. The identification of a novel drug target facilitates breakthroughs in the development of a range of new drugs, ultimately leading to significant social and economic benefits. Moreover, the absence of reported practical applications and registered applications of T3SS inhibitors in agriculture emphasizes the need for future research to focus on studying the target and conducting field experiments to facilitate their practical application in agriculture.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Lu-Lu He: Writing – original draft, Resources, Methodology, Investigation, Data curation. **Lan-Tu Xiong:** Writing – original draft, Resources, Investigation, Data curation. **Xin Wang:** Writing – original draft, Resources, Formal analysis. **Yu-Zhen Li:** Writing – original draft, Investigation. **Jia-Bao Li:** Formal analysis, Data curation. **Yu Shi:** Writing – original draft, Supervision, Funding acquisition. **Xin Deng:** Writing – review & editing. **Zi-Ning Cui:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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