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Bioactivated and selective: A promising new family of nematicides with a novel mode of action

Plant parasitic nematodes (PPNs) are notorious agricultural and forestry pests; they have been estimated to cause over $157 billion USD of crop losses globally every year (Singh et al., 2015). However, the actual damage due to PPNs is likely much bigger than estimated. Wounds produced by PPNs can increase the susceptibility of crops to fungal, oomycete, bacterial, and viral pathogens. Furthermore, many nematode diseases, especially those associated with root-feeding nematodes, are difficult to diagnose and thus poorly managed in developing countries.

COMMERCIAL NEMATICIDES AND THEIR MODES OF ACTION

Synthetic nematicides have been widely used for the control of PPNs for decades. For example, the commercial nematicide fluensulfone causes gradual metabolic damage to nematodes, but the exact target of fluensulfone remains unknown (Figure 1A) (Chen et al., 2020). The amide nematicide fluopyram functions as a succinate dehydrogenase inhibitor to suppress mitochondrial complex II of electron transport chain (Burns et al., 2015), while tioxazafen interferes with ribosomes. However, due to increasing concerns on environmental toxicity and human safety, the availability of commercial nematicides remains very limited. In fact, only less than a hand of nematicides are approved for use in the USA and Europe without restriction in the 20th century (Burns et al., 2023). There is an urgent need for scientists to develop effective nematicides that are safe for the environment and non-target organisms, including fish, yeast, flies, and human beings.

IDENTIFICATION OF A NEW FAMILY OF NEMATICIDES

On May 24th, 2023, an exciting paper that addressed these concerns was published in *Nature* as an article (Burns et al., 2023). In this fascinating paper, Burns et al. used the model free-living nematode *Caenorhabditis elegans* to screen a chemical library for identifying the compounds with nematocidal activity (Burns et al., 2023). Three new imidazothiazole-containing molecules were found to exhibit nematode-killing activity (Figure 1B). The authors designated them as selectivin-A, selectivin-B, and selectivin-C, respectively. These three selectivins specifically kill nematodes, including four free-living nematode species, a nematode parasite of cattle, and the plant parasitic root-knot nematode *Meloidogyne incognita*, while they show almost no toxicity toward non-nematode species including fish, fungi, insects, and human cells.

FIRST-IN-CLASS BIOACTIVATED NEMATICIDES

Considering their high specificity to nematodes, Burns et al. investigated how the nematocidal activity of selectivins is activated (Burns et al., 2023).

Microsomal cytochrome P450 (CYP) enzymes have been found to be often involved in the conversion of dormant pro-drugs into active compounds (Ortiz de Montellano, 2013). Using *C. elegans,* the authors observed that selectivin-A underwent cytochrome-p450-mediated bioactivation to produce γ-glutamylcysteine, glutathione, and cysteine conjugates of an electrophilic sulfoxide metabolite (Figure 1C) (Burns et al., 2023). This kind of bioactivation was highly specific for nematodes because selectivin-A-derived metabolites are either not found or are dramatically reduced in the yeast *Saccharomyces cerevisiae*, the fly *Drosophila melanogaster*, and the fish *Danio rerio*. Consistent with these observations, in the root-knot nematode *M. incognita*, it was found that the CYP enzyme CYP4731A3 bioactivates selectivin-A (Burns et al., 2023).

CONTROL EFFICACIES OF SELECTIVINS ON THE ROOT-KNOT NEMATODE *M. INCOGNITA*

In a tomato field, the authors found that selectivin-A and selectivin-E at 2.5 ppm or 4.5 kg per hectare (kg ha^{-1}) were 43% and 56% effective against the root-knot nematode *M. incognita,* and their control efficacies are comparable to that of the systemic nematicide tioxazafen (Figure 1D) (Burns et al., 2023). It is worthwhile to mention that the authors used a nematode population that is at least two-folder greater than what is considered high density in a tomato field in this test. In terms of selectivity, selectivin-E has no lethal effect on non-target nematodes including the soil-beneficial nematode *Phasmarhabditis hermaphrodita* (Figure 1E).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Besides root-knot nematodes, cyst nematodes (*Heterodera* and *Globodera* spp.), root lesion nematodes (*Pratylenchus* spp.), the burrowing nematode (*Radopholus similis*), the pine wilt nematode *Bursaphelenchus xylophilus*, and the reniform nematode *Rotylenchulus reniformis* were listed as among the top 10 nematodes in molecular plant pathologycausing significant losses to crops

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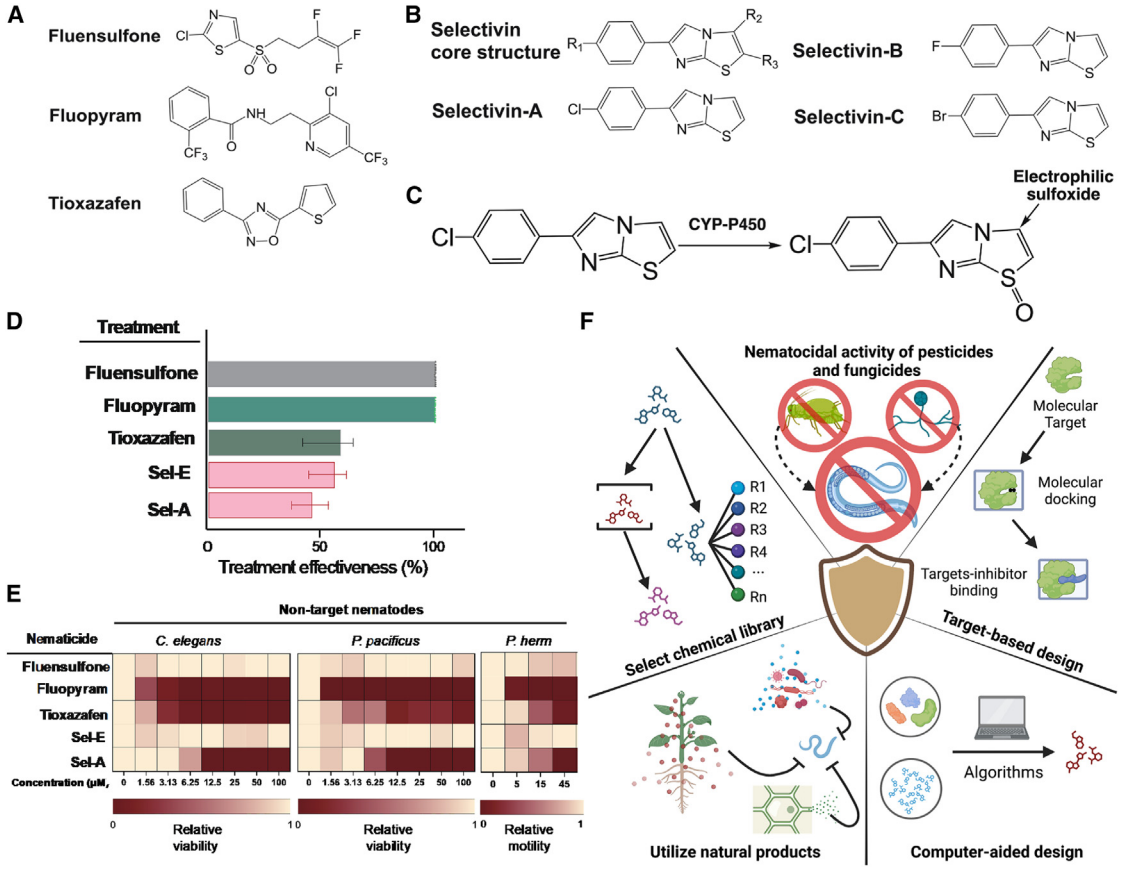

Figure 1. Identification of selectivins as bioactivated and selective nematicides and strategies for the discovery of new nematicides.
(A) Molecular structures of three commercial nematicides fluensulfone, fluopyram, and tioxazafen.
(B) Through screens for nematocidal activity of a chemical library, three selectivins, selectivin-A, selectivin-B, and selectivin-C, were found to exhibit nematode-killing activity.
(C) Selectivin-A undergoes cytochrome-p450-mediated bioactivation to produce a toxic electrophile in nematodes only. In *C. elegans*, γ-glutamylcysteine, glutathione, and cysteine conjugates of an electrophilic sulfoxide metabolite have been detected as selectivin-A-derived products.
(D) Control efficacies of selectivin-A, selectivin-E, fluensulfone, fluopyram, and tioxazafen on the root-knot nematode *Meloidogyne incognita* in a tomato field.
(E) Relative viability of non-target nematodes after they were treated with different concentrations of five nematicides.
(F) Strategies for discovering new nematicides. The figure was created with the software BioRender (BioRender.com).

(Jones et al., 2013). It will be important to test whether selectivins are effective in controlling these nematode diseases.

Burns et al. found that selectivin-A is processed in five nematode species, including *C. elegans* and the root-knot nematode *M. incognita*, to yield γ-glutamylcysteine, glutathione, and cysteine conjugates of a sulfoxide metabolite via CYP-mediated bioactivation (Burns et al., 2023). It remains to be determined whether these products are produced in other PPNs. Currently, it is not clear how selectivins kill *C. elegans* and the root-knot nematode *M. incognita*. Clearly, more studies are needed to find the lethal product(s) of selectivins. Lastly, to further elucidate the underlying mechanism of nematode-killing activity of selectivin-derived metabolites, it will be very helpful to identify their molecular target(s) in PPNs.

In the future, the most potent selectivin derivatives with the strongest nematode-killing activity may be synthesized or slightly modified. These products may achieve higher control efficacies on PPNs than selectivins. Of course, the drawback may be that they may not be as safe as selectivins. Nonetheless, the potential risks of these metabolites on the environment and non-target organisms, especially human beings, need to be fully evaluated.

The success of this approach relies on the utilization of a high-quality chemical library, which already includes active nematicides. Therefore, making the right selections of chemicals and chemical libraries will be critical for the discovery and identification of effective nematicides.

Candidate nematicides can be selected directly from commercial pesticides or fungicides (Figure 1F). For instance, fluopyram was initially registered as a fungicide before it was used as a nematicide (Schleker et al., 2022). Candidate nematicides can also be obtained through computer-aided nematicide design and target-based nematicide design (Chen et al., 2020). The natural alcoholic compound geraniol from plants has good nematocidal activity against *Meloidogyne javanica* and the natural polyacetylene compound falcarindiol from plants show excellent nematocidal activity against *M. incognita* (Ntalli and

Caboni, 2012; Chen and Song, 2021). In addition, extracellular enzymes from microorganisms such as fungi, including serine proteases, chitinases, and collagenases, exhibit nematocidal activities by degrading major components in nematode cuticle and eggshell (Yang et al., 2013). Finally, intermediates or derivatives of lead compounds can also be tested for their nematode-killing activity.

The breakthrough discoveries on selectivins published by Burns et al. open a new avenue for identifying novel nematicides (Burns et al., 2023). Similar approaches may also be developed for discovering new effective pesticides, fungicides, and bactericides, including those that are safe for the environment and human beings.

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