Plant biologists identify promising new fungicides

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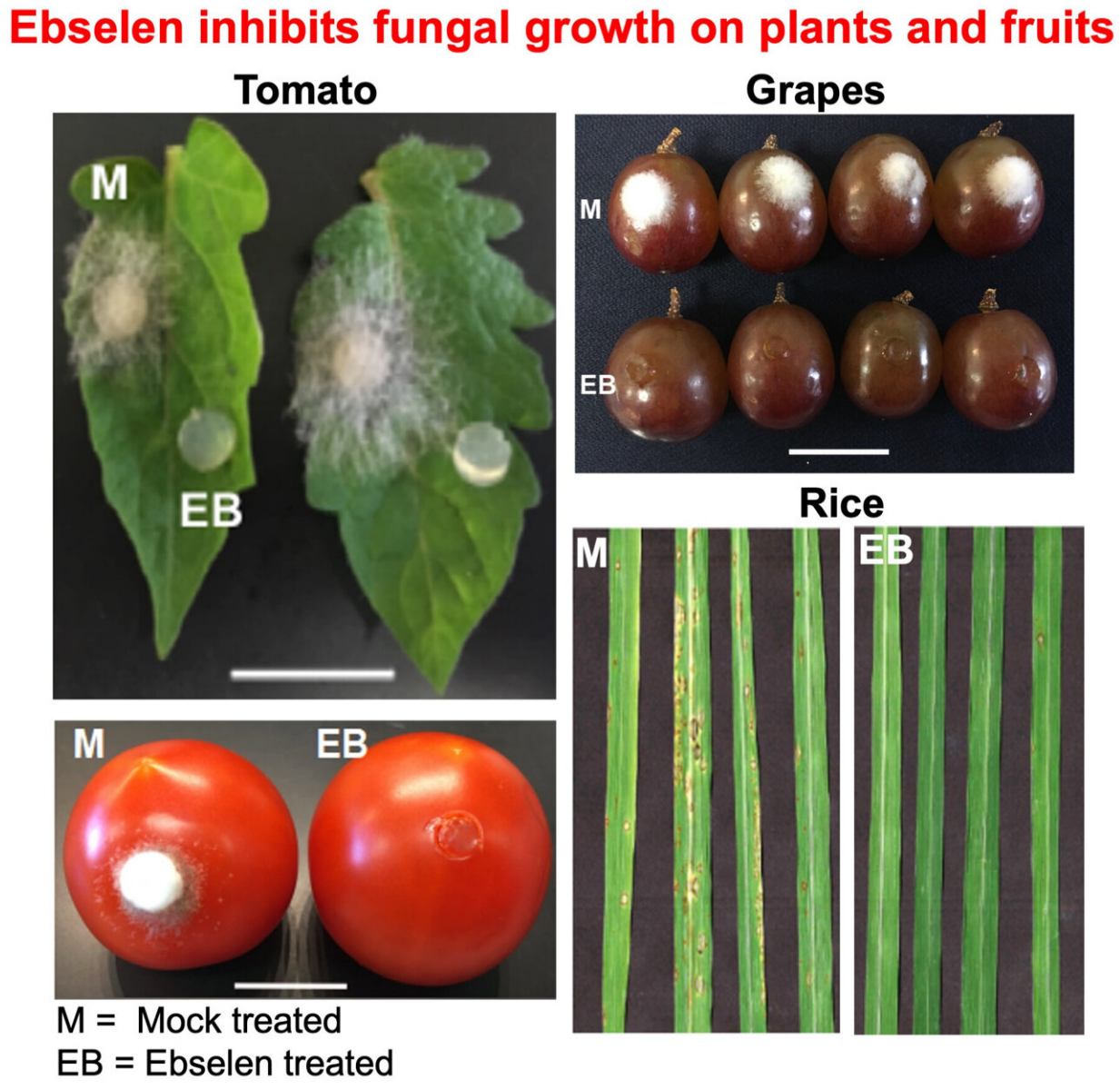

The newly discovered compound ebselen inhibits fungal growth on a variety of plants and fruits, including tomato leaves and fruit, grapes and rice. Credit: UC Davis Department of Plant Biology

A promising new fungicide to fight devastating crop diseases has been identified by researchers at the University of California, Davis. The chemical, ebselen, prevented fungal infections in apples, grapes, strawberries, tomatoes and roses and improved symptoms of pre-existing fungal infection in rice.

Fungal pathogens account for almost a quarter of global crop losses. In the United States, these losses amount to around $150 billion per year. However, fungicide development has been slow for the past 50 years, largely because researchers have had difficulty identifying molecular pathways to target.

In a new study published Feb. 29 in *Nature Communications*, UC Davis researchers identified fungicide candidates that target autophagy, a cellular recycling process that was recently shown as essential for fungal pathogenicity.

Using a novel screening method based on bioluminescence, the researchers identified 30 chemicals that inhibit a key enzymatic step in fungal autophagy. The most promising candidate, ebselen, has been shown to have anti-inflammatory and neuroprotective properties in humans and was more effective at preventing in vitro fungal growth than currently available fungicides.

"Inhibiting autophagy significantly reduces the pathogenicity of several devastating fungal pathogens," said senior author Savithramma Dinesh-Kumar, a professor and chair in the Department of Plant Biology. "Our

findings provide molecular insights that will help to develop the next generation of antifungal compounds."

A novel fungicide target

Autophagy is an essential process in fungi, plants and animal cells that enables them to recycle cellular components and remove toxic waste products. Because recent studies have shown that autophagy is involved in fungal pathogenicity, the researchers hypothesized that blocking autophagy would inhibit fungal infection. They set out to identify chemicals that inhibit autophagy in fungi, focusing on one key step in the pathway—the cleavage of the ATG8 protein by the enzyme ATG4.

To identify chemicals that inhibit this reaction, the team developed a test that allowed them to visualize when the reaction occurred and when it was blocked. Then, they tested the fungi's ability to enzymatically cleave ATG8 in the presence of 2,700 different chemicals from a library of FDA-approved compounds. This method has advantages over other screening methods in that it allows a large number of chemicals to be tested very rapidly.

Altogether, the researchers identified 30 chemical compounds that inhibited cleavage and 14 compounds that enhanced cleavage. They selected the most effective inhibitor, ebselen, for further testing.

Protecting plants from fungal pathogens

In petri-dish experiments, ebselen prevented fungal germination and growth better than drugs that are on the market right now, Dinesh-Kumar said. The team also showed that ebselen prevented fungal infections in a range of plant species while demonstrating curative potential: When the researchers applied the chemical to the leaves of

rice plants that were previously infected with rice blast fungus, it effectively eliminated infection.

"We think ebselen will primarily be useful for protecting plants against future infections, but it can also partially overcome existing infections if it is used early enough," said Dinesh-Kumar.

Although the team's preliminary testing indicates that ebselen specifically inhibits autophagy in fungi, more testing is needed to ensure its safety.

"Since autophagy is highly conserved across different organisms, including humans, more work needs to be done to test the cross reactivity of the drug," said Dinesh-Kumar.

The UC Davis researchers also plan to use their screening method to test even more chemicals for their ability to inhibit autophagy.

"The chemical space is very large, and some chemical libraries have more than 50,000 compounds," said Dinesh-Kumar. "The next step will be to screen for additional autophagy modulators that might help control not just plant fungal pathogens, but also human fungal pathogens."

Correction Note (3/2/2024): The linked publication paper has been updated.

More information: Jongchan Woo et al, Attenuation of phytofungal pathogenicity of Ascomycota by autophagy modulators, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45839-2 , doi.org/10.1038/s41467-024-45839-2

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