# Natural compound found in plants inhibits deadly fungi

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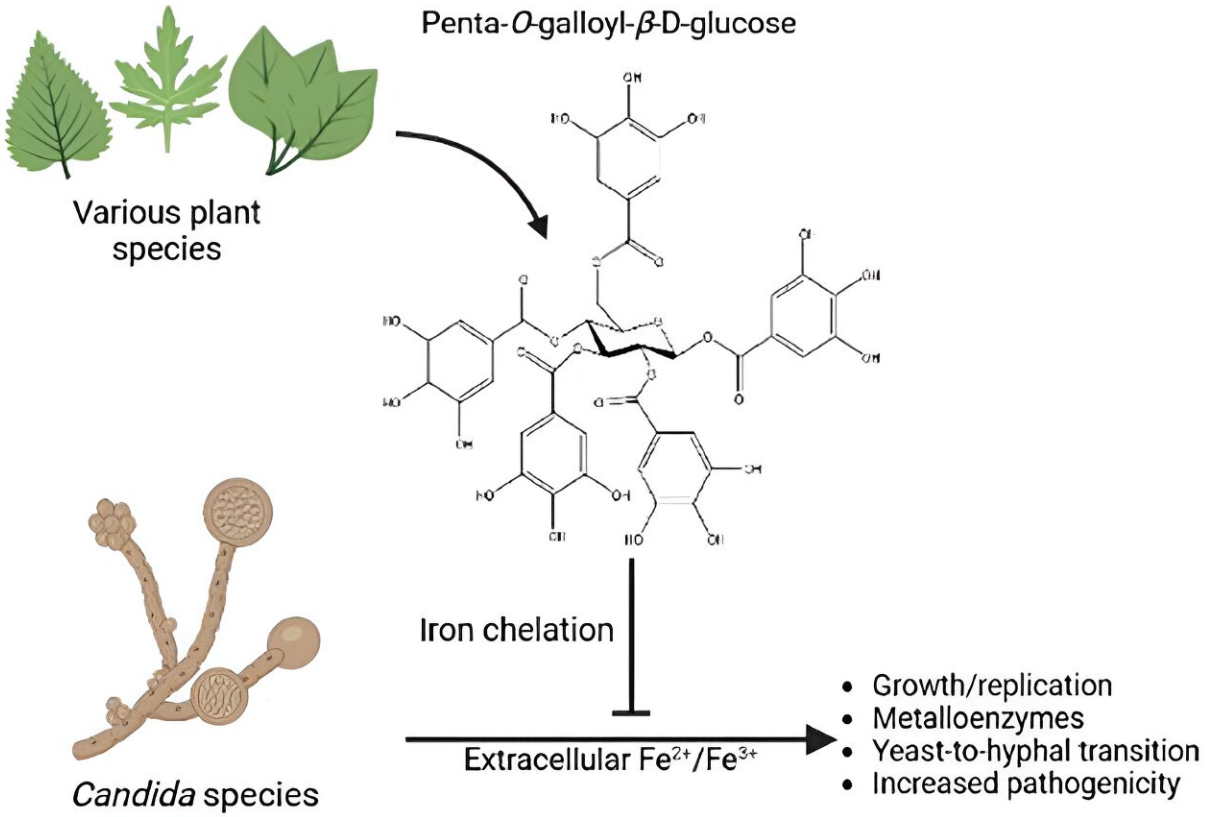


Credit: *ACS Infectious Diseases* (2023). DOI: 10.1021/acsinfecdis.3c00113

A new study finds that a natural compound found in many plants inhibits the growth of drug-resistant Candida fungi—including its most virulent species, Candida auris, an emerging global health threat. The journal

*ACS Infectious Diseases* published the discovery led by scientists at Emory University.

Laboratory-dish experiments showed that the natural compound, a water-soluble tannin known as PGG, blocks 90% of the growth in four different species of Candida fungi. The researchers also discovered how PGG inhibits the growth: It grabs up iron molecules, essentially starving the fungi of an essential nutrient.

By starving the fungi rather than attacking it, the PGG mechanism does not promote the development of further drug resistance, unlike existing antifungal medications. Laboratory-dish experiments also showed minimal toxicity of PGG to human cells.

"Drug-resistant fungal infections are a growing health care problem but there are few new antifungals in the drug-development pipeline," says Cassandra Quave, senior author of the study and assistant professor in Emory School of Medicine's Department of Dermatology and the Center for the Study of Human Health. "Our findings open a new potential approach to deal with these infections, including those caused by deadly Candida auris."

C. auris is often multidrug-resistant and has a high mortality rate, leading the Centers for Disease Control and Prevention (CDC) to label it a serious global health threat.

"It's a really bad bug," says Lewis Marquez, first author of the study and a graduate student in Emory's molecular systems and pharmacology program. "Between 30% and 60% of the people who get infected with C. auris end up dying."

"It's challenging but interesting to work on the forefront of natural product drug discovery," says Emory graduate student Lewis Marquez, first author of the study. He is shown during a Quave lab field trip to Ichauway in south Georgia. Credit: Emory University

## An emerging threat

Candida is a yeast often found on the skin and in the digestive tract of healthy people. Some species, such as Candida albicans, occasionally grow out of control and cause mild infections in people.

In more serious cases, Candida can invade deep into the body and cause infections in the bloodstream or organs such as the kidney, heart or brain. Immunocompromised people, including many hospital patients,

are most at risk for invasive Candida infections, which are rapidly evolving drug resistance.

In 2007, the new Candida species, C. auris, emerged in a hospital patient in Japan. Since then, C. auris has caused health care-associated outbreaks in more than a dozen countries around the world with more than 3,000 clinical cases reported in the United States alone.

## A 'natural' approach to drug discovery

Quave is an ethnobotanist, studying how traditional people have used plants for medicine to search for promising new candidates for modern-day drugs. Her lab curates the Quave Natural Product Library, which contains 2,500 botanical and fungal natural products extracted from 750 species collected at sites around the world.

"We're not taking a random approach to identify potential new antimicrobials," Quave says. "Focusing on plants used in traditional medicines allows us to hone in quickly on bioactive molecules."

Previously, the Quave lab had found that the berries of the Brazilian peppertree, a plant used by traditional healers in the Amazon for centuries to treat skin infections and some other ailments, contains a flavone-rich compound that disarms drug-resistant staph bacteria.

Screens by the Quave lab had also found that the leaves of the Brazilian peppertree contain PGG, a compound that has shown antibacterial, anticancer and antiviral activities in previous research.

A 2020 study by the Quave lab, for instance, found that PGG inhibited growth of Carbapenem-resistant Acinetobacter baumannii, a bacterium that infects humans and is categorized as one of five urgent threats by the CDC.

The Brazilian peppertree, an invasive weed in Florida, is a member of the poison ivy family.

"PGG has popped up repeatedly in our laboratory screens of plant compounds from members of this plant family," Quave says. "It makes sense that these plants, which thrive in really wet environments, would contain molecules to fight a range of pathogens."

## Experimental results

The Quave lab decided to test whether PGG would show antifungal activity against Candida.

Laboratory-dish experiments demonstrated that PGG blocked about 90% of the growth in 12 strains from four species of Candida: C. albicans, multidrug-resistant C. auris and two other multidrug-resistant non-albicans Candida species.

PGG is a large molecule known for its iron-binding properties. The researchers tested the role of this characteristic in the antifungal activity.

"Each PGG molecule can bind up to five iron molecules," Marquez explains. "When we added more iron to a dish, beyond the sequestering capacity of the PGG molecules, the fungi once again grew normally."

Dish experiments also showed that PGG was well-tolerated by human kidney, liver and epithelial cells.

"Iron in human cells is generally not free iron," Marquez says. "It is usually bound to a protein or is sequestered inside enzymes."

## A potential topical treatment

Previous animal studies on PGG have found that the molecule is metabolized quickly and removed from the body. Instead of an internal therapy, the researchers are investigating its potential efficacy as a topical antifungal.

"If a Candida infection breaks out on the skin of a patient where a catheter or other medical instrument is implanted, a topical antifungal might prevent the infection from spreading and entering into the body," Marquez says.

As a next step, the researchers will test PGG as a topical treatment for fungal skin infections in mice.

Meanwhile, Quave and Marquez have applied for a provisional patent for the use of PGG for the mitigation of fungal infections.

"These are still early days in the research, but another idea that we're interested in pursuing is the potential use of PGG as a broad-spectrum microbial," Quave says. "Many infections from acute injuries, such as battlefield wounds, tend to be polymicrobial so PGG could perhaps make a useful topical treatment in these cases."

**More information:** Lewis Marquez et al, Potent Antifungal Activity of Penta-O-galloyl-β-d-Glucose against Drug-Resistant Candida albicans, Candida auris, and Other Non-albicans Candida Species, *ACS Infectious Diseases* (2023). DOI: 10.1021/acsinfecdis.3c00113

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