Compounds extracted from Brazilian savannah plant combat fungus that causes candidiasis

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Four substances isolated from Mimosa caesalpiniifolia were found to be more effective against thrush and candida than was fluconazole, the drug usually prescribed to treat the disease. Brazilian researchers are developing an ointment. Credit: Marcelo José Dias Silva

Fungi of the genus *Candida* cause thrush and candidiasis, a fairly common disease in humans. It can be lethal to individuals with low immunity, especially when they are hospitalized. Although the drug most widely used to combat the disease is effective in most cases, some varieties of the fungus are drug-resistant.

Compounds that combat two species of *Candida* have now been isolated from a plant by researchers based in Brazil and Spain. The plant is *Mimosa caesalpiniifolia*, a shrub native to the Cerrado (Brazilian savannah) and called sansão-do-campo, sabiá or cerca-viva in Portuguese. The idea is to create an ointment for use as an alternative to fluconazole, long considered the best antifungal for candidiasis, which can cause itching and pain in the genitals, vaginal discharge, and sores in the mouth or elsewhere.

The results of the research, which was supported by São Paulo Research Foundation—FAPESP, are published in the *Journal of Natural Products*. The investigation was conducted during Marcelo José Dias Silva's postdoctoral fellowship at São Paulo State University's Bioscience Institute (IB-UNESP) in São Vicente, Brazil. Silva did part of it while he was at the University of Cádiz (UCA) in Spain, also with a scholarship from FAPESP.

The study was led by principal investigator Wagner Vilegas, full professor at IB-UNESP. The group also received funding from the Spanish Ministry of the Economy, Industry and Competitiveness.

"This discovery and the development of novel therapeutic entities, which in the right combination could lead to a considerable reduction in the necessary concentration of drugs, can minimize the side effects and toxicity of the antimicrobial agents in conventional use," Vilegas said.

"The final cost of treatment can also be reduced, as can the resistance acquired by some microorganisms. More research is needed, including both prospection studies like this one and studies using biological models."

Ointment

A total of 23 known compounds were isolated from *M. caesalpiniifolia*, as well as five new flavonoids named mimocaesalpin A, B, C, D and E. Applied to samples of *Candida glabrata* and *C. krusei*, four of the 28 compounds displayed more effective antifungal activity than did fluconazole.

"We applied the different compounds to these two fungi, and most had little or no effect. However, four showed promising activity and will be tested in the form of ointments," said Silva, first author of the article.

Three formulations will be tested, using the compounds or combinations found to be most effective in inhibiting fungal growth, including a combination of a type of beta-sitosterol with ethyl gallate. These two substances are present in several plant species and are particularly abundant in *M. caesalpiniifolia*.

Another formulation will contain one of the new flavonoids, mimocaesalpin C. The third will combine this mimocaesalpin with beta-sitosterol.

"Beta-sitosterol on its own was not effective, but when combined with

the other two compounds, it was synergistic and highly effective. Mimocaesalpin C displayed promising selective activity against *C. krusei*, which is resistant to fluconazole," Silva said.

Before arriving at these candidate medications, however, the researchers produced an extract from the plant and submitted it to chromatography fractionation, a laboratory technique for separating a mixture into its components.

Five fractions were produced in this manner and tested for antifungal activity. Three fractions inhibited fungal growth by 50%. These more promising fractions were then subjected to the same technique to isolate the new flavonoids and other compounds.

"*M. caesalpiniifolia* extract is very complex. It contains a large amount of chlorophyll and fatty acids, all of which hinder the identification of the compounds present. Thanks to our partnership with colleagues at the University of Cádiz, we were able to separate them out and focus our investigation on the most viable fractions," Silva said.

Before creating the ointments, the researchers will perform tests to determine whether the antifungal effect of the four compounds persists or even increases when they are mixed with adjuvants, substances used to enhance the efficacy or potency of a medication in the organism.

More information: Marcelo J. Dias Silva et al, Bioassay-Guided Isolation of Fungistatic Compounds from Mimosa caesalpiniifolia Leaves, *Journal of Natural Products* (2019). DOI: 10.1021/acs.jnatprod.8b01025

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