New method allows scientists to screen natural products for antibiotics

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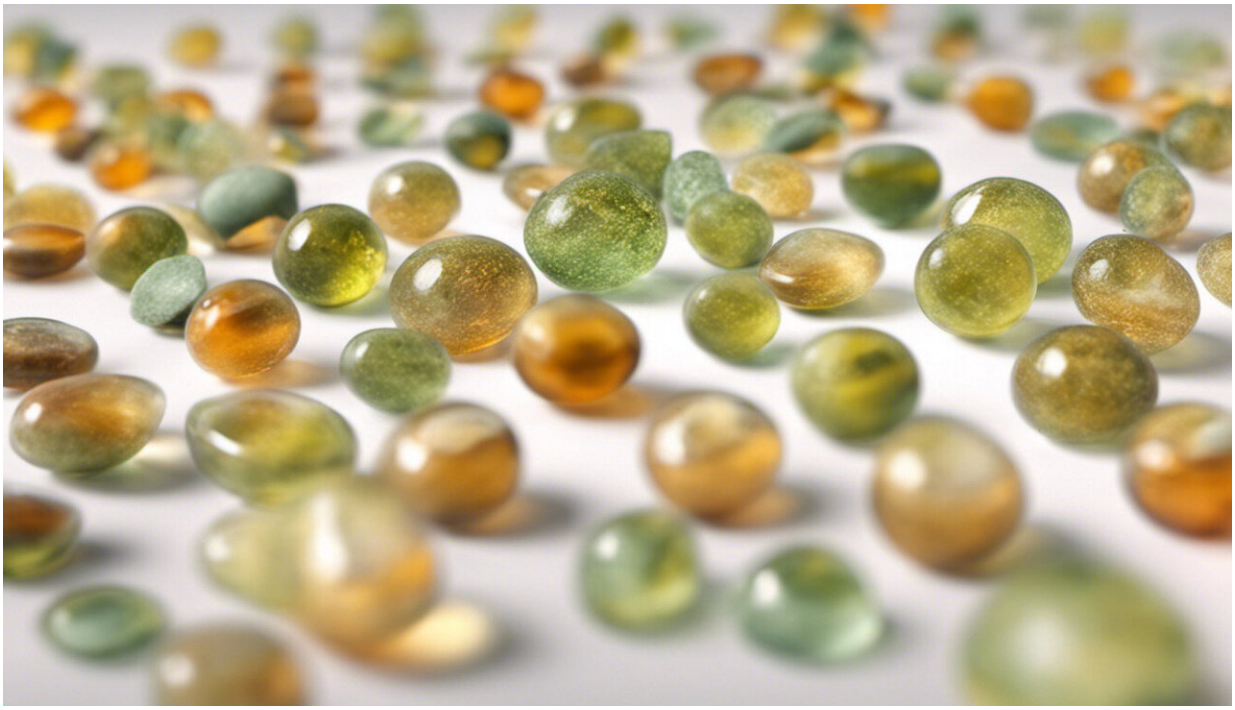

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Biologists at UC San Diego have found that a method they developed to identify and characterize new antibiotics can be employed to screen natural products quickly for compounds capable of controlling antibiotic resistant bacteria.

The researchers, who published their findings in this week's edition of the *Journal of Antibiotics*, say their latest discovery could permit chemists and others to understand how mixtures of potential antibiotics from microorganisms work without first purifying them. It builds on their development two years ago of a new way to rapidly identify new compounds capable of killing bacteria.

"Our initial discovery allowed us to perform the equivalent of an autopsy on bacterial cells and is changing the way industry searches for new antibiotics from collections of pure chemicals," said Kit Pogliano, a professor of biology at UC San Diego who headed the research team. "But we didn't know if it would work for identifying antibiotics found in natural product extracts, which are very complex mixtures frequently filled with multiple types of antibiotics."

"We've now shown that our method is a powerful way to identify antibiotics from natural products and understand how they work before they are ever purified," she added, "potentially shaving years off of screening efforts by identifying which organisms and growth conditions produce interesting bioactive molecules."

Most of the world's clinically useful antibiotics are derived from molecules referred to as natural products because they are naturally produced by microorganisms. This includes penicillin and streptomycin, the first two antibiotics widely used clinically beginning in the 1940's. As pathogens evolved resistance to penicillin and streptomycin, new natural product antibiotics were needed.

During the 1950's and 1960's, a large number of antibiotics were discovered. But after 75 years of intensively screening microbes for antibiotics, scientists appear to have harvested all of the easy to find antibiotics. Attempts to find antibiotics from natural products now often result on the repeated isolation of one of the hundreds of molecules that

have been already discovered.

Further frustrating the effort is that traditional approaches for isolating natural product antibiotics require molecules that have killing activity to be purified before performing extensive experiments to determine how they work, said Joe Pogliano, a professor of biology at UC San Diego and a co-author on the study.

"This is a very slow, labor intensive process that typically requires many months of effort, and frequently ends with discovering that the molecule does not have a new or interesting mechanism of action," he added. "Our method solves this problem by providing a new way to find a unique needle in a haystack of needles. Before any of the time-intensive work has been started, we can determine which samples have an activity that is new or interesting."

"This method is a powerful tool for identifying new compounds from sources of natural products that kill bacteria and for determining how they work," noted Kit Pogliano. "Some bacteria have evolved resistance to every known class of antibiotic and, when these multi-drug resistant bacteria cause an infection, they are nearly impossible to treat. There is an urgent need for new antibiotics capable of treating infections caused by antibiotic resistant bacteria."

Antibiotic resistance is increasing at an alarming rate. The Review on Antimicrobial Resistance, a publication established to produce an analysis of the global problems of antimicrobial resistance, recently predicted that by 2050, the worldwide toll from drug resistant bacterial infections could reach 10 million deaths per year, more than cancer (8.2 million) and diabetes (1.5 million) combined.

"New molecules capable of killing drug resistant pathogens by new mechanisms are desperately needed," said Joe Pogliano.

According to the Centers for Disease Control and Prevention, antibiotic-resistant strains of Carbapenem-Resistant Enterobacteriaceae, or CRE, were found to cause infections in patients in nearly 200 hospitals in the United States alone.

"Since these bacteria are resistant to all antibiotics, close to one-half of patients die from these infections," said Joe Pogliano. "Recent work shows that bacteria resistant to colistin, a last line of defense, are common in farm animals in China. The gene for colistin resistance can be easily spread to other bacteria, making it likely that colistin resistance will become widespread in the future."

Over the last 25 years, the number of new antibiotics entering the clinic has drastically declined. At the same time, bacteria have continued to evolve resistance to all of the currently available drugs, creating the current critical situation. One of the main problems in identifying new antibiotics and bringing them to market is a lack of understanding how the molecules work.

"It's easy to identify microbes that produce antibiotics that kill bacteria," explained Kit Pogliano. "The difficult part is determining which microbes produce a new molecule with a new activity. With our new method, we can determine which strain is producing an interesting activity and then follow that specific activity during purification to make sure we purify the right molecule. This new approach will help to open up the discovery pipeline, allowing more potential antibiotic producing strains to be rapidly screened for antibiotics that are active against multidrug resistant bacterial pathogens."

The UC San Diego biologists say their new method promises to revolutionize how natural product antibiotic discovery teams guide their studies. With traditional methods, understanding how an antibiotic works requires purified or at least partially purified molecules.

"Our new method represents the first time that the mechanism by which one microbial strain kills another can be determined without purifying the molecules involved," said Poochit Nonejuie, a postdoctoral fellow in biology who is also a co-author of the paper.

Pogliano said her research team, which also included Pieter Dorrestein, a professor of pharmacology at UC San Diego, will be continuing to search for antibiotics.

"We are now using this method to look for new antibiotics from unique collections of microbes to find those that are active against antibiotic resistant bacteria," she said.

This technology is being commercialized by Linnaeus Bioscience Inc., which allows the pharmaceutical industry access to the method.

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