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Looking to Nature for New Sunscreens

Melissa Pandika

A growing group of researchers believes photoprotective compounds from algae and other organisms could soothe consumers' concerns.

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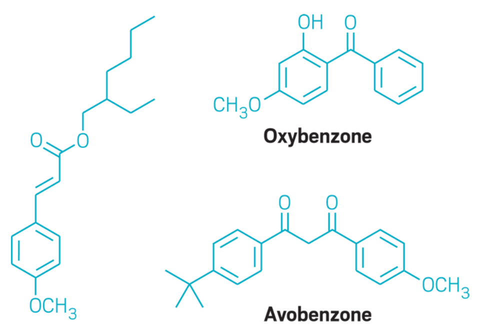
Sunscreen users may feel burned if they do and burned if they don't: Concerns about the health and environmental effects of current sunscreens seem to be making consumers warier about using them and lawmakers more likely to restrict them. Some sunscreen compounds approved by the U.S. Food & Drug Administration, for instance, have recently fallen under scrutiny for their potential to disrupt hormone signaling, which is linked to increased cancer risk. And in July, the governor of Hawaii signed a bill to ban in-state sale of sunscreens containing either oxybenzone or octinoxate, suspected to harm coral reefs. Meanwhile, around the world skin cancer rates are on the rise: 132,000 cases of melanoma and 2 to 3 million cases of other skin cancers occur each year.

Inventing and approving new sunscreen compounds with fewer downsides could alleviate concerns and increase use, but cosmetic chemists working in this area have their work cut out for them, particularly in the U.S. The FDA is notoriously slow in approving sunscreen compounds, requiring exhaustive evidence of their safety. Indeed, FDA has approved only 16 sunscreen ingredients, while other areas of the world, like the European Union and Australia, have approved nearly twice as many.



Still, a growing cadre of scientists is banking on Mother Nature to help satisfy both consumers and regulators. In recent years, these researchers have embarked on a quest to develop naturally derived sunscreen compounds. While some researchers are extracting them from their natural sources, others are engineering yeast or other organisms to produce them. Still others are designing synthetic analogs of these compounds. The hope is that their natural origins will alleviate worries from all corners.

ANSWERS FROM THE SEA

Sunlight transmits two types of ultraviolet radiation that can cause skin damage: UV-A rays, which are linked to skin aging and may contribute to some forms of skin cancer, and higher-energy UV-B rays, which can cause sunburns, as well as skin cancer. Ingredients in sunscreen can protect skin from UV rays in two ways. Some inorganic compounds, like titanium dioxide and zinc oxide, form a physical barrier, acting like tiny mirrors that deflect UV rays, whereas organic compounds like avobenzone and oxybenzone have chemical bonds that absorb UV radiation and dissipate it as less-harmful heat.

Nature employs similar modes of protection, especially in photosynthetic organisms that rely on sunlight for energy yet also need to protect themselves from the harmful UV radiation it contains. In some plants, a thick, waxy cuticle forms a physical barrier that deflects UV rays. But organisms, like algae, that lack this physical barrier use other forms of photoprotection—for instance, a chemical defense, says Yousong Ding, a medicinal chemist at the University of Florida's College of Pharmacy. It's these chemical defenses that have captivated Ding and others. "We look to nature to see how it has solved the problem."

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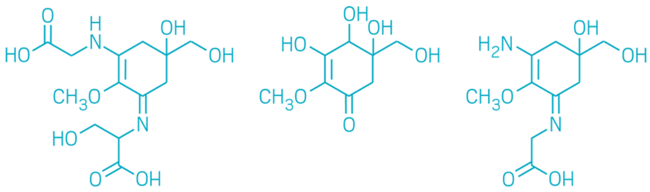
Marine organisms deploy one such chemical defense: mycosporine-like amino acids (MAAs), a family of compounds that consist of a core cyclohexenimine or cyclohexenone ring with various functional groups attached. Scientists trace these compounds' sun-protection capabilities to their conjugated double bonds, thought to absorb high-energy UV radiation and dissipate it as heat, as the organic compounds in commercially available sunscreens do. MAAs make for attractive candidate sunscreen ingredients: They're low molecular weight, water soluble, and stable when exposed to light or heat.



Shinorine **Gadusol** **Palythine**

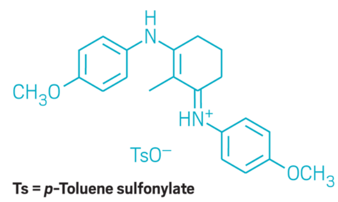
Ding has engineered a cyanobacterium to produce an MAA called shinorine. Two European companies already sell sunscreen containing shinorine extracted from *Porphyra umbilicalis*, a type of red algae; the problem is that this species can take more than a year to grow before it can be harvested and the MAA extracted. So Ding's team turned to synthetic biology. The researchers combed the genome of the cyanobacterium *Fischerella*, which also produces shinorine, to find the shinorine synthesis genes. Then they overexpressed these genes in *Synechocystis*, a cyanobacterium that takes only 2 weeks to yield enough shinorine to harvest. Under UV-B light, shinorine-expressing *Synechocystis* cells showed greater growth than *Synechocystis* without the shinorine genes, suggesting shinorine had protected them from UV-B damage. "A few companies are contacting us to see how to commercialize our technology," Ding says, though he won't specify which ones.

Researchers led by Taifo Mahmud of Oregon State University's College of Pharmacy have found that some vertebrates, including zebrafish, produce a compound called gadusol that's structurally related to MAAs and protects against UV-B. Mahmud and his team inserted the gene cluster responsible for gadusol into yeast. Their engineered yeast churned out gadusol, lowering the cells' sensitivity to UV-B light. Since then, the researchers have launched a spin-off company, Gadusol Laboratories, and received a National Science Foundation grant to further boost the yeast strain's yield.

■ (SLIGHTLY) SYNTHETIC SOLUTIONS

Nature's sunscreens have appeal, concedes Diego Sampedro, an organic chemist at the University of La Rioja, but he remains skeptical that they can be produced economically, with or without genetic tools.

Even if the engineered microorganisms are making a lot of a sunscreen compound, "in the end, they're living organisms," and the compound still needs to be purified from the soup of proteins and other stuff the yeast produce, he says. To sidestep this process, Sampedro and his team use natural sunscreen compounds merely as a starting point and instead chemically synthesize analogs of these compounds. Using computer modeling, they designed a bare-bones template compound that included only the components of MAAs "absolutely necessary" for UV protection, he explains. They saw that an aminocyclohexenimine core had properties that made for a good sunscreen, including strong UV absorption and an ability to remain stable when exposed to light. Next, they used this template to develop a suite of analogs that are relatively simple to produce at larger scales. Adding them to commercial sunscreens boosted the products' ability to protect against UV-A and UV-B rays in standard tests.



Representative synthetic mycosporine-like amino acid analog

But others think that being able to say that a compound is "natural" is central to any new suncreen's success. "Consumers do not want anything genetically modified or synthetic," even if it started out as a natural compound but was derivatized, says Paul Long of the Institute of Pharmaceutical Science at King's College London.

Last year, Long and his colleagues showed that an MAA called palythine, which is extracted from the red algae *Chondrus yendoi* that can be harvested year-round, protected lab-grown human skin cells from UV-A and UV-B damage under artificial sunlight as intense as at noon in the Arizona summer. The team filed a patent application for palythine and licensed it to a London-based skin care company, which plans to release a product containing it as the active ingredient later this year.

Marine organisms aren't the only ones that protect themselves from the sun's harmful rays. Recently, other Oregon State University researchers have turned to the wildflower meadowfoam for sunscreen inspiration. With delicate white blossoms, meadowfoam is native to the Pacific Northwest and is cultivated for its oil as an ingredient in shampoos and beauty products. The oil extraction process leaves behind lots of plant waste called seed meal, which is a rich source of glucolimnanthin, a glucosinolate compound. The researchers knew from earlier work that a glucosinolate

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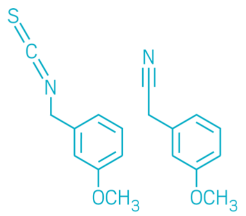
derivative—sulforaphane—was photoprotective, so they decided to investigate whether derivatives of the glucolimnanthin in seed meal could offer photoprotection, too.



Glucolimnanthin derivatives

In a study published in May, the team, led by Arup Indra and Gitali Ganguli-Indra of OSU's College of Pharmacy, showed that these derivatives might reduce UV-B damage. Specifically, in three-dimensional cell culture models of skin, the compounds prevented the DNA cross-linking triggered by UV-B, which can lead to cancer-causing mutations. They also blocked the activity of enzymes that degrade collagen, the protein that plumps and firms skin, hinting that they may also have antiaging properties.

Meadowfoam seed oil is already commercially available, which suggests mass production of the glucosinolate derivatives is also "completely feasible," Indra says. In fact, meadowfoam seed oil producer Natural Plant Products has agreed to supply the seed meal to Indra and colleagues, who will then prepare the extract and isolate the glucolimnanthin derivatives. The 2018 meadowfoam harvest could yield nearly 13 t of one derivative and 10 t of the other, according to Natural Plant Products CEO Mike Martinez, though the process is still only at the lab scale. "I wouldn't be surprised if it replaced traditional chemical sunscreens," Indra contends.

■ THE BIGGEST HURDLES

Before that can happen, Mahmud says, researchers need to demonstrate—for any of these compounds—that at a minimum they offer comparable protection from the damaging effects of sunlight and safeguard against UV-B rays over the same amount of time as currently available compounds. Indra for one, says he and his colleagues plan to test how the UV protection of meadowfoam derivatives measures up against that of zinc oxide or titanium dioxide. Beyond that, the health and environmental impacts need testing too: The compounds' natural origins don't exempt them from controlled studies of these properties. Long, who is commercializing palythine from red algae, is optimistic that marine compounds should be safe. They are found in seaweed and marine animals that have been part of our diets, he notes, and they already exist in the marine environment so are unlikely to be damaging.

From there, the problem of cost-effective manufacturing would need to be solved to compete with today's standard ingredients.

But even with new compounds in hand, FDA remains a huge hurdle. As close as palythine is to commercialization, Long says he and his team have no immediate plans to break into the U.S. market, dissuaded by the time and expense that go into gaining FDA approval. "All the trials they require, the bureaucratic holes you have to go through" are daunting, he says. Whereas the EU considers sunscreens cosmetics and Australia puts most sunscreens in the category of low-risk medicines that aren't subject to evaluation before they hit the market, the U.S. considers them drugs that need to undergo safety and effectiveness testing.

As a result, sunscreen ingredient options in the U.S. lag behind those in other parts of the world, says David Steinberg, president of Steinberg & Associates, a cosmetic and topical over-the-counter drug compliance consultancy. The active sunscreen ingredients that are available in other countries absorb UV radiation better and are required in lower levels, so they feel better on the skin. "Absolutely, we need new UV filters," Steinberg says, but naturally derived compounds won't have a shorter road to FDA approval than any other new compounds companies might want to bring to market. They all still face the same protocol required for getting new drugs approved. Being natural "doesn't make them better."

But assuming these compounds do go to market, Mahmud envisions adding them alongside already available compounds to start, rather than replacing them. "For a while, perhaps we won't replace zinc oxide and titanium dioxide but use the new compounds with them. Perhaps using them together would give an optimal effect." Since these compounds differ in their UV defense mechanisms, a combination may ensure more comprehensive protection.

Although the prospects of these new sunscreen compounds remain unclear, Mahmud sees no signs of the search abating. "It's a growing field," he says. As the number of melanoma cases rises amid a tenuous regulatory landscape, "more and more people are paying attention" to the development of naturally derived sunscreen compounds. And with consumers caring more than ever about the products they use and where they end up afterward, he says, demand for them will only grow.

Melissa Pandika is a freelance contributor to Chemical & Engineering News, the weekly news magazine of the American Chemical Society.

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