

reaction is primarily important as a model reaction, although it might eventually prove technically relevant in the purification of various gas streams containing minor carbon monoxide impurities. However, during the last decade, more examples of aerobic oxidations of other substrates have been reported over gold nanoparticle catalysts (11). Several of these reports have targeted potentially interesting large-scale industrial chemicals, such as gluconic acid (12), acetic acid (13), and propylene oxide (14). For such reactions, it is highly desirable to use air as the oxidant and have pure water as the only side product. With proper catalysts available that feature both high activity and selectivity, this can be considered the ultimate way to conduct oxidations (see the figure). Even though the gold catalysts have shown promising performance

in these reactions, they have apparently not been competitive with existing technologies. Accordingly, some studies have attempted to improve the catalytic activity and selectivity—for example, by proper alloying (11) or by strategies to prolong the catalyst lifetime (15). Wittstock *et al.* specifically show how silver alloying promotes oxygen activation, and how the unsupported, nanoporous gold catalysts are stable for prolonged test runs (2). It is tempting to assume that this type of catalyst could also prove beneficial in some of the aerobic oxidation reactions in which only supported pure gold catalysts have been tested until now. Possibly, this will take green gold catalysis closer toward industrial applications.

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PLANT SCIENCE

The Botanical Solution for Malaria

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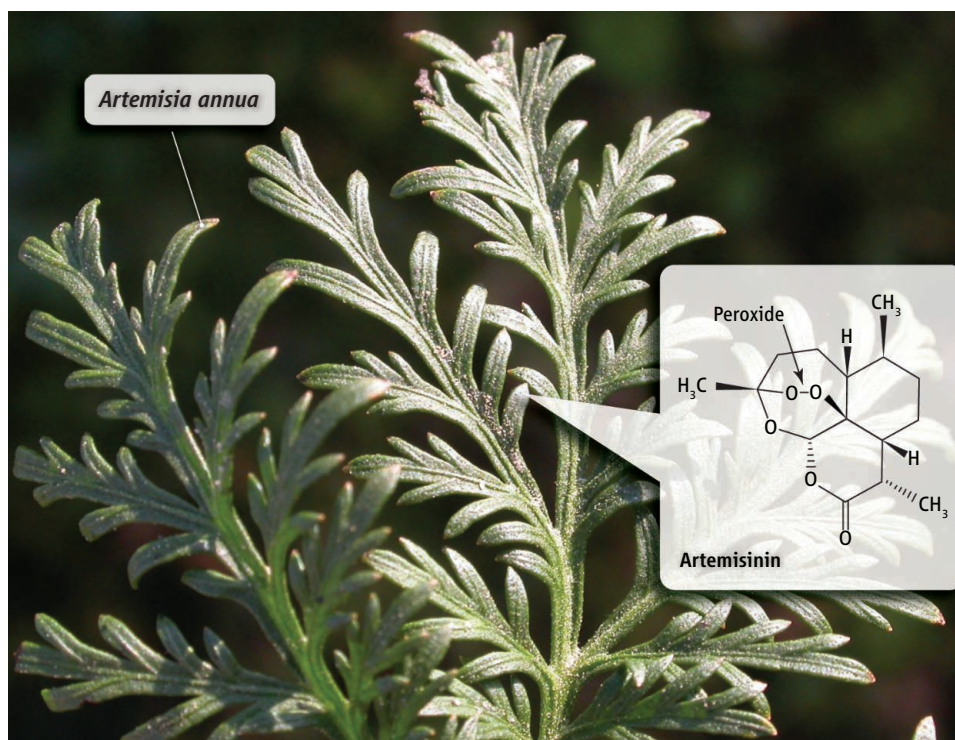
For thousands of years, Chinese herbalists used leaves from the plant *Artemisia annua* to treat numerous illnesses, including malaria. Today, the plant's natural antimalarial compound—a sesquiterpene lactone (and endoperoxide) called artemisinin—is the most effective drug for combating malarial infections (see the figure). A major hurdle in using this compound to treat malaria—estimated to cause 300 to 500 million cases and over 1 million deaths each year, worldwide—has been producing enough artemisinin to meet world demand. Attempts to efficiently extract sufficient quantities have been slowly improving. Now Graham *et al.* (1) have paved the way to fast-track breeding varieties of the *A. annua* plant with highly desirable genetic traits. On page 328 of this issue, the authors report a genetic map of the plant and identify key loci that could improve agricultural yields, decrease production costs, ensure a steady global supply of the drug, and improve grower confidence in the crop.

Graham *et al.* recognized that the yield of artemisinin varied by geographic origin and was inheritable when the super leafy strains possessing bountiful glandular trichomes—outgrowth structures where artemisinin is produced and stored by the plant—were crossed.

They used a pedigree plant (*Artemis*) to establish the first genetic linkage and quantitative trait loci (QTL) maps for the plant species, and then validated positive QTL for artemisi-

Improved breeding of a plant that produces a major antimalarial compound is now possible based on knowledge of its genetic map.

nin yield. The authors used deep sequencing of the plant transcriptome (all mRNA molecules present in the organism) to successfully identify genes and markers, which will



Natural drug resource. The antimalarial compound artemisinin is purified from the plant *Artemisia annua*. Information about the plant's genetic map should allow for breeding and selection of agronomic traits that will enable rapid development of improved varieties.

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facilitate crossing of highly productive varieties. Their results are innovative in terms of the scale of research and sophistication of the technologies involved.

This seminal result comes almost 25 years after artemisinin crystals were first reported in 1985 by Klayman (2). This achievement was pivotal because it also broke a code, but a medicinal chemistry process code rather than a genetic one. Prior to this report, only Chinese scientists could crystallize the purified compound from the plant source. Unfortunately, they would not share their technology with the Western world at that time.

Klayman assembled botanists from the Smithsonian Institute, and located a small naturally growing *A. annua* “crop” on the banks of the Potomac River. However, this discovery came at a low point for drug development at the Walter Reed Army Institute of Research, where scientists, including Klayman, were struggling with a slimmed down research budget—reduced from over \$70 million (adjusted for inflation) per year during the Vietnam War era, to \$4 million in the 1980s. Ironically, during the same period, the Vietnam government asked China for the Qinghaosu (Chinese word for artemisinin) miracle to combat malaria that had become resistant to other drugs. Another shocking blow to the Walter Reed effort was the discovery of brainstem lesions in animal models during advanced preclinical toxicology testing of drug candidates (3). It would take years to unravel the mystery of this neurotoxicity. Millions of dollars were spent to prove an

acceptable safety profile of the water-soluble forms of the compound, such as artesunate and arteminate, over the lipid-soluble forms such as artemether or arteether (4). Finally, in 2004, a regulatory dossier was filed with the U.S. Food and Drug Administration (FDA) and artesunate was made available to treat severe and complicated malaria in the United States (5). Just last year, the FDA approved an oral artemisinin combined therapy for less severe cases.

The artemisinin yield from Klayman’s 1985 Potomac River variety of *A. annua* was only 0.06% of dry weight of plant material, whereas the Chinese had described varieties in Sichuan province with yields of 0.01 to 0.5% (2). Even the best of basic crop science, though, would not keep pace with the growing global health demands and emerging resistance to the antimalarial mainstay, chloroquine. Solid financial backing and entrepreneurship by the Bill and Melinda Gates Foundation and the Medicines for Malaria Venture (an international public-private partnership) would prevail with a three-pronged strategy extending into 2015: Develop synthetic artemisinin-like peroxides that are easy and inexpensive to make and lack potential cross resistance to other drugs, exploit microbial-based systems that promote synthesis of the artemisinin precursor for chemical conversion to the mature form, and use innovative horticulture technologies to boost plant robustness and production. However, these strategies have had variable success. While thousands of synthetic artemisinin com-

pounds have been made and tested, only a select few have been stable, orally available, and efficacious in animal models (6). The Medicines for Malaria Venture prioritized the development of next-generation compounds (ozonides), however, initial clinical efficacy trials were disappointing, and efforts refocused on molecules with improved druglike properties (7). Production of recombinant artemisinin in bacterial and yeast systems have experienced success, but still require at least three synthetic steps to achieve the final product (8, 9).

So far, the strategy that has produced the most promise for the near term, and will likely provide the most cost-effective final product of this life-saving drug, rests with innovative horticultural technologies. The result of Graham *et al.* has placed us on that track. The next big hurdle for this molecule will be emerging resistance to the drug.

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CHEMISTRY

Ion Chemistry Mediated by Water Networks

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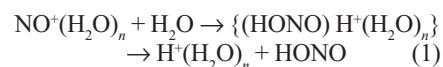
The remarkable properties of liquid water derive largely from its ability to form fluctuating networks of hydrogen bonds. However, even in the gas phase, where clusters of only a few water molecules may form, their sparse hydrogen-bonded networks may still absorb energy and stabilize reactants and products (1–3), stabilize intermediates as catalysts (1), or act as reaction part-

ners. In the D region of the ionosphere (70 to 85 km above Earth), the positively charged ions that form there, such as NO⁺, can formally transfer charge to one water molecule and add an OH⁻ group to form a neutral species (such as HONO). The resulting protonated water networks (4–7) are regarded as the major positive-charge carrier in the D region, which is the lowest ionospheric layer that affects radio communications. On page 308 of this issue, Relph *et al.* (8) report on a combined experimental and theoretical study that tries to unravel the relation between the hydrogen-bonding arrangement of a set of

The reaction of ions such as NO⁺ with networks of only a few water molecules has implications for understanding chemistry in the ionosphere.

water molecules around an NO⁺ ion and the chemical activity of this ensemble. Their results bear on a key open question: Are there particular water clusters that account for most of the reactivity?

The key processes in this reaction



involve water clustering around the NO⁺, charge separation, and finally the elimination of nitrous acid (HONO) and production of the H⁺(H₂O)_n “cations” (reaction 1). NO⁺

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