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LOOKING TO NATURE FOR NEW THERAPIES

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

Tinkering: Azithromycin was synthesised by adding one nitrogen atom to the structure of erythromycin A. | Photo Credit: Getty Images

Progress in medicine requires a steady pipeline of new therapeutics with desirable biological activities. An optimistic view holds that the rapid strides made on several technological fronts would make it easier to discover and formulate new drugs.

An increased understanding of disease processes at the molecular level has yielded a long list of potential drug targets. Computer-aided “Rational Drug Design”, the making of these designed drug candidates by organic chemists, followed by high throughput screening — where automation is used to test drug candidates — should aid in new discoveries. Yet, the pace of introduction of new drugs has not matched expectations.

The natural world around us is a time-tested source of new therapeutics — traditional systems of medicine have relied on natural sources for several millennia. Natural products are chemicals that are found in plants and microorganisms that dwell in soil and water.

From the first clinical trial of an anti-cancer drug in 1946 until 2019, 40% of all approved anti-cancer drug molecules were either substances found in nature, or derived from natural products. For the period 1981-2019, half of the 162 new antibacterial therapeutics are either pure natural products or nature-derived, meaning they are designed in laboratories, but are close relatives of molecules seen in nature (Newman and Cragg, *Journal of Natural Products*, 2020). An example is the antibiotic Azithromycin. It was first synthesised by chemists in Zagreb, Croatia, who cleverly added one new nitrogen atom to the structure of the naturally occurring and commonly used antibiotic erythromycin A. The resulting drug had fewer side effects than erythromycin, and is among the most widely prescribed antibiotics today.

On the other hand, all the 14 antihistamine drugs presented as new chemical entities to the U.S. Food and Drug Administration between 1981 and 2019 are synthetic inventions (e.g., cetirizine).

Many potent natural products are present in vanishingly small amounts in their native state, making it difficult to collect enough of the molecule for laboratory investigations. They also occur along with dozens of other chemical entities, so pinpointing the molecule of interest is not straightforward, and requires laborious separation procedures. One way out is to synthesise quantities of an interesting molecule after preliminary results show promise.

An instance of a new drug candidate from a natural source that has been traditionally used as medicine has been recently published (Woo and Shenvi, *Nature*, 2022). On the island of Papua New Guinea in the South Pacific, the Galbulimima tree yields a bark that has for long been used for treating pain and fevers. It is also used in rituals because it is hallucinogenic. When combined with the leaves of the Homalomena shrub, it is psychotropic, inducing a serene dream-like state that is followed by a tranquil sleep. Homalomena (*sugandhmantri* in Hindu, and *merugu* in Tamil) is found in India, and has been traditionally used for various ailments.

Galbulimima has intrigued medicinal chemists for several decades, and 40 unique alkaloids have been identified in extracts from this tree. Alkaloids are nitrogen-containing organic compounds found in many plants, e.g., quinine and nicotine.

Woo and Shenvi worked out an efficient way of synthesising the alkaloid GB18, which has a complex geometry. Their method produces gram quantities of GB18. In the bark, its concentration is measured in parts per million. Tests showed that it is an antagonist of opioid receptors.

Opioid receptors in human body are found in the nervous system and the digestive tract. Our bodies make natural opioids, such as endorphins that bind to these receptors and tone down the transmission of pain signals. Endorphins, thus, have analgesic properties, similar to opiates such as morphine. Endorphins also induce a sense of feeling good, of euphoria, which is a rewarding experience. Both these factors help explain the addictive potential of substances that trigger your opioid receptors.

GB18 does not influence the sensation of pain, but has cognitive effects — mice devote less time to grooming behaviors such as smoothening out their fur and whiskers.

The last antagonist of opioid receptors to be discovered, 35 years ago, was naltrexone. Sold in India under brand names such as Nodict and Naltima, it is used in the management of addiction to opioids as well as to alcohol. And as opioid receptors are also associated with the digestive system, naltrexone helps in weight reduction in the obese.

What will be the uses of GB18 and its many possible derivatives? Much work lies ahead, and many tantalising therapeutic possibilities.

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