CHEMICAL ECOLOGY IN RELATION TO MEDICINE AND PHARMACEUTICALS

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Summary

To date many human diseases have no cure, and several ancient human diseases have emerged as resistant to current drugs or increased their undesirable side effects. The pharmaceutical industry needs to search constantly for new drugs to solve these problems. It is in the quest for new bioactive molecules that the approach to this search diversifies. The chemical study of natural products, ethnobotanics, and biotechnology, and research into chemical synthesis and the combinatorial chemistry technique have

helped to discover and produce new drugs to combat human diseases. Chemical ecology is a new and alternative way to look for new medicines based on interrelations between organisms that are mediated by molecules. While biochemical science explores the chemical processes that take place within an organism, chemical ecology explores the chemical processes occurring within nature. Not only may a large diversity of bioactive compounds be isolated from chemical ecology studies but also, even more importantly, these kinds of studies show the "chemical strategy" developed by different organisms that enables them to manipulate the biochemical machinery of other organisms (for example in parasitism, symbiosis, and so on). Since the molecules identified from chemical ecology studies are known to have some kind of bioactivity, it gives a starting point advantage in the search for new medicines.

1. Introduction

The twentieth century brought great progress in the battle for human health, and led to the belief that at least infectious diseases could be eliminated. Unfortunately, most microorganisms involved in human diseases are becoming resistant to antibiotics, and there is widespread concern about the emergence of new infectious diseases, such as HIV, as well as biochemical diseases (diabetes, Alzheimer, and so on). Moreover, in industrialized countries, the incidence of other health problems related to social interactions (stroke, stress), or diet (high cholesterol), and the like has increased and requires more effective treatments. Thus, there is a need for pharmaceutical industries to extend the search for new drugs and there is also interest in the development of new drugs with fewer side effects.

From ancient times humankind has extracted a number of drugs from plants to treat various human diseases. Phytochemical studies use success–failure assays to find a new drug. However, when there is no previous information about the activity of a compound, random screening natural products for trial has had a low rate of success. Ethnobotanic studies offered an alternative approach to the search for new drugs or leads, by researching products that have long been used as traditional remedies for different illnesses by indigenous cultures.

Another way to search for new drugs and leads is the chemical synthesis of compounds. The classical synthetic compounds and combinatorial chemistry techniques have produced an increment in the number of new chemical structures, by creating compound libraries and testing them rapidly for desirable properties instead of analyzing single molecules at a time. However, these modern methods have not produced as many positive results as the pharmaceutical industries had hoped, and have sometimes had unpredicted negative consequences. For example, some reports indicate that a number of synthetic products that replace sugar, and that are widely consumed by diabetics, may cause a number of side effects such as seizures, loss of memory, and joint pain. Since the biological activity of new synthetic molecules is unknown, a larger number of studies over longer time periods are necessary, increasing the costs for pharmaceutical industries. This is also true for "natural" compounds. Ethnobotany has the advantage of drawing attention to plants that have a history of healing properties within a given culture; once bioactive molecules have been identified within a given medicinal plant, however, their properties and toxicity must be reassessed in the new product. For example, kava (a plant from the family of black pepper) is a herbal drink of the South Pacific with antidepressant powers that has become popular in European countries and in the United States. Unfortunately, its use has been banned recently in those same countries because of hepatotoxicity reports, although differences in the way kava is prepared in Europe as opposed to the traditional preparation may have something to do with this problem.

Chemical ecology offers alternative methods to search for new drugs, based on the study of a number of interactions among organisms, such as predator–prey, parasite–host interactions, and sexual attraction. These interactions are mediated by biochemical compounds (pheromones, antifeedants, and so on), which are produced and released by the organisms involved. From an understanding of the chemical processes participating in such interactions, bioactive molecules can be extracted and evaluated in the prevention, diagnosis, and treatment of human diseases.

In the following sections some examples of the potential of chemical ecology studies for the discovery and development of new medicines and ways to prevent diseases in humans are described.

2. Chemical Defenses

2.1. Anti-Predator Mechanisms

Preys have developed a large diversity of strategies to evade predation, including mobility, distasteful/toxic secretions, warning color patterns or vocalization, and mimicking of the environment. The development of physical and chemical defenses to avoid predation is particularly relevant to sessile organisms, as they cannot move. They must develop strategies to recover from the damage inflicted by a predator, and to prevent future attacks.

Terrestrial plants represent the most important group among sessile organisms. Plant predators are very diverse (mollusks, arthropods, mammals, birds), and in turn plants have evolved a wide diversity of chemical defenses with different physiological effects. Among the bioactive compounds produced by plants are the isoflavones, a group of compounds related to flavonoides, mostly found in Leguminosae (soybean, alfalfa, and so on). Australian sheep farmers first observed the estrogenic effect of isoflavones when their herds became infertile and showed some anticoagulant problems after feeding on clover pastures. This effect was also observed in natural bird populations that fed on legumes that diminished their reproductive success. Thus, isoflavones have sufficient estrogenic activity to seriously affect the reproduction of grazing animals, acting as a tool for population control of herbivores. The estrogenic activity is the result of mimicking the shape and polarity of the steroid hormone oestradiol. Used medically, the estrogenic effect of isoflavones can give some protection against estrogen-dependents such as breast cancer and have potential to protect against degenerative diseases such as heart disease. Genistein, a principal soy isoflavone, has recently aroused interest in medical research due to its numerous biochemical properties including inhibition of the activity of tyrosine-specific protein kinases and topoisomerase II, and estrogenic and antioxidant activity as well as anti-proliferative and anti-angiogenic effects. Moreover, genistein has been shown to inhibit the growth of human prostate cancer cells by affecting the cell cycle and inducing apoptosis, and potentiating the effect of radiation on prostate carcinoma cells.

The chemical defenses of many organisms involve compounds that inhibit the development and/or differentiation of their predators. In insects, molting and other developmental events leading to the metamorphosis from larval to the adult stages are regulated by the steroid hormone ecdysone. The phytoecdysones are a group of compounds produced by plants that mimic ecdysones, and occur regularly in primitive plants such as ferns, especially in *Polypodiaceae,* in gymnosperms, especially *Taxaceae* and *Podocarpaceae,* and less frequently in angiosperms. Phytoecdisones disrupt the development of insects that might devour them, and may cause developmental aberrations such as the development of multiple head capsules that can block their mouthparts. These types of compounds may be used for the control of insects that are vectors of diseases.

Arthropods, and particularly insects, can incorporate chemical compounds from their prey for their own benefit (see Figure 1). These compounds can either be stored in their original configuration or may be chemically modified. Chemical medicine is interested not only in the molecules that are modified, but also in the specific groups that are incorporated, and in the comparison between the original and new biological function. For example, female *Photuris* fireflies sequester steroidal pyrones and lucibufagins from male fireflies of the genus *Photinus* that they eat, and transform the sequestered lucibufagins both by glycosylation and oxidation. After feeding on *P. ignitus* males, *Photuris* females contain novel lucibufagin that gives them protection against jumping spiders that would otherwise prey on them. From a point of view of medicinal chemistry, the modified lucibufagins have shown large potential as antiviral compounds in infectious diseases studies.

Figure 1. *Ruta graveolens* is a perennial herb traditionally known to have several healing properties. It produces several chemical compounds including glycosides, furocoumarins, alkaloids, and essential oils that serve as anti-predator defenses by repelling some insects, but also attracting others, including a number of butterflies and their parasitoid wasps.

Another classical example of anti-predator mechanism is the monarch-butterfly–*Asclepias* host plant association. *Asclepias* produce toxic compounds such as cardiac glycosides to defend themselves against predation, but monarch larvae have developed the capacity to sequester those toxins and pass them on to the adults. Those toxins provide the monarch butterfly with protection against predatory birds, because any bird attempting to eat them will vomit and learn to avoid eating any insect resembling the monarch in the future. The defensive compounds synthesized by some *Asclepias* species have medicinal uses as expectorants and pain relievers, and have mild purgative properties.

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Biographical Sketch

Julio Alberto Zygadlo was born in 1957 in Argentina, where he completed his doctorate in Biological Sciences at the Universidad Nacional de Córdoba (UNC) in 1989. He has held a variety of teaching positions at the UNC. He was Visiting Professor of Complutense University, Spain, in 1994. Currently he is Assistant Professor of Organic Chemistry and Natural Products at the Instituto Multidisciplinario de Biologia Vegetal (IMBIV-CONICET). His research draws on areas such as natural compounds, and plant–insect, and plant–plant interaction. So far, he has worked on potential pharmaceutical applications of terpenes. He has described the essential oil composition and bioactivities of many aromatic plants of Argentina. He has published a range of articles in scientific journals about natural products and chemical ecology, and has been a contributing author to books in Phytochemistry and Pharmacology.

Raquel Miranda Gleiser was born in the United States of America but grew up in Argentina, where she completed her doctorate in Biological Sciences at the Universidad Nacional de Córdoba (UNC). She has held a variety of teaching positions at the UNC, CRILAR, and the Universidad Nacional de La Rioja. Currently she is at the Department of Pathobiological Sciences, School of Veterinary Medicine, Louisiana State University (USA) undertaking post-doctorate research on the ecology of arbovirus, and teaching. Most of her research experience is in medical entomology. Among her major research accomplishments she has shown that temporal variations in abundance of mosquitoes in Argentina may be monitored using meteorological satellite imagery. She has published several articles in scientific journals about mosquito surveillance and ecology, and has been a contributing author to a book on medical entomology. Her professional interests include understanding the ecology of arthropods of medical and veterinary importance, arbovirus transmission, and pest control.