GUEST EDITORIAL

Dr. István Ujváry, born 1953. Senior research scientist, Chemical Research Center, Hungarian Academy of Sciences (HAS), Budapest, Hungary. Dipl. Chemical Engineering (1977), Ph.D. in Organic Chemistry (1995) (both at the Technical U. of Budapest). 1977–82, research scientist, EGIS Pharmaceuticals, Budapest; 1982–99, senior research scientist, Plant Protection Inst., HAS; 2000– , senior research scientist, Chemical Research Center, HAS. Visiting scientist: 1984, Dept. of Zoology, U. of Washington, Seattle, WA; 1987–89, Dept. of Chemistry, U. of New York at Stony Brook, Stony Brook, NY; 1989–90, Dept. of Environmental Sciences, Policy and Management, U. of California, Berkeley, CA; 1996–97, USDA-ARS, College Station, TX, all USA. *Research grants:* from the HAS, Hungarian Scientific Research Fund, National Office of Technology and Development, American–Hungarian Joint Research Fund, European Union, IAEA. *Past and current interests:* chemistry and toxicology of synthetic and natural pest control agents; synthesis of radiolabeled insect hormones for receptor studies; insect pheromones and attractants; carborane-containing compounds; environmental contaminants; BIOSTER database for drug design; drugs of abuse. Editorial board member of *Pest Management Science*. *Awards:* HAS Award for Young Investigators (1987). Author and co-author of over 70 research publications; inventor or co-inventor of 21 patents.

Transforming Natural Products into Natural Pesticides – Experience and Expectations

The history of agriculture comprises a nearly 10,000-year fight with destructive animals, weeds and plant diseases to protect crops. Until the early 20th Century, cultural and mechanical methods augmented by a diverse range of organic and inorganic substances derived from plants, animal and minerals (13) dominated pest control. While many traditional natural pest control agents (natural pesticides, hereafter NPs) still remain in use, especially local plant preparations on rural farms in developing countries, their limited supply and sometimes low efficacy could not fulfill the growing needs of intensive farming. Effective and affordable synthetic pesticides gained ground by the mid-20th Century, due to the maturing chemical industry. Nevertheless, natural products are still contributing to pest control in many ways: (i) in their own right either as crude extracts or in purified form (2,19), *e.g.* pyrethrins, *Bt* δ-endotoxins, bilanafos, gibberellins, essential oils, and polyoxins; (ii) as starting materials for semisynthetic derivatives, *e.g.* emamectin, dihydroazadirachtin; (iii) as lead molecules for synthetic analogs, *e.g.* pyrethroids and strobilurins; (iv) as research tools in pharmacological studies, *e.g.* α-bungarotoxin; and (v) as exploration tools in the discovery of new modes of action, *e.g.* hormones.

The annual global pesticide market has been around US$30 billion with NPs accounting for only a small percentage of the sales, although exact data are not available. In order to appraise the overall impact of natural products on the pesticide industry and agriculture, I examined the currently marketed active ingredients (3,17) according to their origin and development history (Table 1). On the whole, roughly 10% of all crop protection chemicals are genuine natural products. In the insecticide class, over one-third of the active ingredients are either natural products or (semi)synthetic descendants thereof (see also ref. 1). Note that the individual counting of the species-selective sex pheromones and attractants (21 listed in the literature sources examined) inflates the share of NPs. Of the analogs, pyrethroids predominate. Among herbicides, synthetics discovered by random screening prevail, but analogs of plant hormones – such as auxin – and of other plant growth regulators are also important. The 12 herbicide safeners, invented to alleviate phytotoxicity of various herbicides to crops, are entirely of synthetic origin. The rodenticide palette is made up mostly of natural products, *e.g.* ergocalciferol, strychnine, and analogs of the anticoagulant dicumarol isolated originally from spoiled sweet clover.

TABLE 1. Active ingredients of various classes of pest control agents and related agrochemicals according to their origin[z]

Class	Natural products	Synthetic organics		Inorganics (incl. organometallics)
		Natural product analog[y]	Other organics	
Insect control agents	55 (20)	56 (20)	159 (58)	6 (2.2)
Weed control agents, incl. herbicide safeners, and plant growth regulators	9 (2.9)	31 (9.9)	265 (85)	8 (2.6)
Plant disease control agents	9 (5.2)	7 (4.0)	144 (83)	14 (8.0)
Rodent control agents	6 (30)	10 (50)	3 (15)	1 (5.0)
Others				
vertebrate repellents			2	1
molluscicides			3	1

[z] Based on refs. 3 and 17. Numbers in parentheses indicate % of the total chemical entities in that activity category (due to rounding, the sum does not equal 100%).

[y] Obtained either by modifying bioactive 'foreign' natural product templates or by biorational design using the structure of the target organism's endogenous substances, such as hormones.

Several natural products with pesticidal activity could not be developed into useful NPs because of (i) insufficient level of activity against economically important pests; (ii) inappropriate activity spectrum; (iii) insufficient field stability; (iv) production cost (both economic and ecological); and (v) lack of patentability.

When scarcity of a natural substance necessitates, chemical synthesis is a viable alternative for structurally simple NPs, *e.g.* insect pheromones. Alternatively, for complex molecules such as the antiparasitic doramectin, directed biosynthesis can be used whereby unnatural synthetic precursors serve as feedstock for fermentation; naturally selected mutants or genetically engineered microorganisms are also promising approaches (5,9).

What makes NPs unique in comparison with synthetic pesticides? Are they privileged over synthetics in terms of bioactivity? According to recent studies that analyzed and compared the structural properties of natural products and of synthetic substances in computer databases (Chapman & Hall's *Dictionary of Natural Products* and MDLI's *Available*

Chemicals Directory, respectively) (7,14), natural products tend to have: (i) more oxygen atoms, often as ring-connected alcohol and ether groups (*e.g.* azadirachtin); (ii) fewer nitrogen atoms, although this is at odds with the insecticidal properties of many alkaloids (18); (iii) fewer halogen atoms; (iv) more polar regions; (v) fewer aromatic systems but more non-aromatic C=C double bonds; (vi) greater abundance of sp^3-hydridized bridgehead atoms; and (vii) more chiral centers. A related study applied this approach to design synthetic scaffolds based on natural products, *e.g.* anisomycin (15).

The structural and physicochemical dissimilarity of synthetic and natural bioactive substances manifests itself in another respect. The so-called Lipinski's 'Rule of 5' is a set of empirical rules taking into account the molecular weight, lipophilicity, H-bond donor and acceptor properties of orally bioavailable pharmaceuticals (10), but it does not apply to drugs of natural origin. It has also been shown that the 'Rule of 5', when adapted to agrochemicals, has good predictive power for most synthetic insecticides but fails for natural insecticides (16), demonstrating again the unusual features of natural products. These findings confirm the indispensable role of traditional, large-scale screening approaches in pesticide discovery.

Natural products are not just interesting chemicals with elaborate structures that organic chemists, being unable to design them, select to sharpen their synthetic tools, but substances with remarkable biological properties. Living organisms have evolved intricate offensive and defensive systems for survival. It has been generally accepted, though rarely proven, that such bioactive substances provide ecological advantage. Some natural products are active against only a few organisms, while others affect many. On the biochemical–pharmacological level a single component can have more than one molecular target, thus functioning as a multipurpose defense substance (20). Furthermore, natural products typically occur as a cocktail of metabolically related compounds (Nature's combinatorial library) with differing activity spectra. The complexity of crude extracts explains the versatility of many popular ethnobotanical preparations, *e.g.* of the neem tree. Synergistically acting mixtures could be advantageous in practice in terms of efficacy and pest resistance management but this is seldom exploited due to pesticide regulations requiring costly toxicity assessment of each individual active ingredient (see *e.g.* ref. 8).

Insufficient selectivity, occurrence of resistance towards many pesticides, environmental and human health concerns, as well as the emergence of new pests, have been fueling the search for NPs and other, biology-based control technologies, including biopesticides (2,4). However, one has to bear in mind that although NPs are renewable, their production is not without cost or environmental impact.

The traditional sources of NP discovery have been plants and microorganisms and undoubtedly these will continue to yield promising substances. Current intensive research on plant essential oils, mainly as alternative fumigants for stored-product pest insects and pathogens, will certainly bear fruit. Animals, arthropods in particular, have already provided tools for insect control (*e.g.* juvenoids), but newer substances from this source (*e.g.* neuropeptides and various venoms) still hold promise. Less is known about pesticidal natural products of mammalian organisms, let alone those of human origin. Research on marine and fresh water organisms has also uncovered some NP prototypes (*e.g.* nereistoxin), but these reservoirs have barely been tapped.

It is reasonable to expect that random screening of natural extracts will uncover novel NP candidates from time to time. Recent examples are the insecticidal spinosyns and the entomopathogenic *Photorhabdus* bacterium, as well as the fungicidal pyrrolnitrin and strobilurin analogs. In the age of ecology and information technology, the exploitation of chemical signals for pest management will increase in importance beyond the already successful use of insect pheromones. Advances in genomics will facilitate the discovery and development of new NPs, particularly in the manipulative use of plant–herbivore (11), plant–plant (12) and plant–pathogen (6) interactions. Genomic-based approaches will certainly revitalize the microbial product arena by enhancing the biosynthetic capabilities of microorganisms, *e.g.* through heterologous expression of complex biosynthetic pathways leading to enriched and tailored chemical diversity.

Since the major part of Nature's already existing chemical diversity waits to be discovered, one can enthusiastically say "you ain't seen nothin' yet".

István Ujváry
Institute of Chemistry, Chemical Research Center
Hungarian Academy of Sciences
H-1025 Budapest, Hungary
[Fax: +36-1-325-7554; e-mail: istvan@chemres.hu]

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