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Invited Paper

Chemicals from nature for weed management

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Natural products represent a vast repository of materials and compounds with evolved biological activity, including phytotoxicity. Some of these compounds can be used directly or as templates for herbicides. The molecular target sites of these compounds are often unique. Strategies for the discovery of these materials and compounds are outlined. Numerous examples of individual phytotoxins and crude preparations with weed management potential are provided. An example of research to find a natural product solution of a unique pest management problem (blue-green algae in aquaculture) is described. Finally, the problems associated with natural products for pest control are discussed.

Key words: Allelochemicals, aquaculture, blue-green algae, biological activity, natural products, phytotoxins.

Natural products have been the source of many pesticides, used either directly as crude preparations or as pure compounds. Rather than being used directly, they have been used more often as structural leads for the discovery and development of natural product-based pesticides. There are more examples of natural product use as fungicides, insecticides, and other pesticides than as herbicides (Pachlatko 1998). However, there are some success stories with herbicides, and natural products remain part of the herbicide discovery strategy for those companies that still have a herbicide discovery program.

The rationale for natural products in a herbicide discovery strategy has several disparate components. Nature is full of bioactive materials and compounds with unexploited properties. Many of the hundreds of thousands of secondary products generated by plants, microbes, and animals are the result of coevolution of the producing organism with pests. Thus, the compounds have biological activity. Sometimes, the function of the compound in nature is as a phytotoxin, as with phytotoxins produced by plant pathogens or allelochemicals produced by allelopathic plants. However, very often biocides with a specific function in nature can be used for quite different purposes, as with many natural product-based pharmaceuticals. In short, biological activity is more certain with secondary compounds from nature than with randomly synthesized compounds.

Improved instrumentation has considerably reduced the cost of isolation and identification of natural compounds from what it was a decade ago. This has caused renewed interest in natural products in herbicide discovery programs. Another major reason for interest in natural phytotoxins is that they often have novel sites of action (Duke et al. 2000b, 2000d) (Table 1). Even if the phytotoxin is unsuitable for commercial use, identification of a new molecular target site can be very valuable in the design of synthetic herbicides. Natural compounds or preparations may require less regulatory scrutiny for registration than synthetic compounds, thus reducing the cost of commercializing the product. In some market niches, such as the home garden, the claim that a pesticide is "natural" will appeal to the consumer. In other markets, synthetic herbicides are either not allowed (organic gardening) or unlikely to have long-term approval (e.g., certain aquaculture situations). Lastly, despite the relatively low priority of natural products in herbicide discovery, there have been some major successes with natural products as herbicides or herbicide leads (described later). Successes lead to greater interest.

This review will discuss research strategies and the most important successes. Some interesting examples of natural products that have not made it to the market will also be provided, with the reasons that some of these products were unsuccessful. Several recent general reviews of natural products as potential herbicides are available (Dayan et al. 1999b; Duke et al. 1998, 2000b, 2000d, 2002; Hoagland 2001; Hoagland and Cutler 2000). Other reviews concentrate on microbial compounds as herbicides (Abbas and Duke 1997; Duke et al. 1996; Saxena and Pandey 2001) or the modes of action of natural phytotoxins (Duke et al.

TABLE 1. Molecular target sites of highly phytotoxic natural products.

Compound	Molecular target site[a]
AAL-toxin (a toxin from *Altemaria alternata*)	Ceramide synthase
Actinonin	Peptide deformylase
Brefeldin	Golgi apparatus function
Carbocyclic coformycin	Adenosine monophosphate deaminase
Cerulenin	3-ketoacyl-acyl-carrier protein synthase
Cochlioquinones	Mitochondrial reduced nicotinamide adenine dinucleotide reductase
Coronatine	Jasmonic acid antagonist
1,4-cineole	Asparagine synthetase
Fisherellin	*D-1 protein of photosystem II*
Fumonisin	Ceramide synthase
Fusicoccin	Plasma membrane adenosime triphosphatase (ATPase)
Gabaculin	Many transaminases
Gostatin	Aspartate amino transferase
Grandinol	*D-1 protein of photosystem II*
Hydantocidin	Adenylosuccinate synthase
Leptospermone	*4-Hydroxyphenylpyruvate dioxygenase*
Phaseolotoxin	Ornithine carbamoyltransferase
Phosphinothricin	Glutamine synthetase
Podophyllotoxin	*Tubulin*
Prehelminthosporol	Plasma membrane ATPase
Pyridazocidin	*Energy diversion from photosystem* I
Quassinoids	Nicotinamide adenine dinucleotide phosphate oxidase?
Rhizobitoxin	β-Cystathionase
Tagetitoxin	RNA polymerase
Sorgoleone	*D-1 protein of photosystem II*
Syringotoxin	Plasma membrane ATPase
Tentoxin	CF_1 ATPase of the chloroplast
Tricolorin A	Plasma membrane ATPase
Thiolactomycin	Acetyl-CoA transacylase
Usnic acid	*4-Hydroxyphenylpyruvate dioxygenase*

[a] Molecular target sites in italics are shared by synthetic herbicides.

1997, 2000c). Reviews of the general concept and strategies for utilizing natural products as pesticides are available (Rice et al. 1998). In this paper we shall update the material from these previous reviews and attempt to widen the scope of the coverage to include crude preparations and minor uses, such as natural products as algicides in aquaculture. However, this short review provides only a sampling of what is known about the potential use of natural products for weed management.

Discovery Strategies

Known Compounds

Hundreds of thousands of natural compounds have been isolated and their structures elucidated, but relatively few of these have been adequately tested for phytotoxicity. Rather than randomly bioassaying known compounds, structural and activity clues can be used to maximize chances of finding phytotoxic compounds.

Using Structural Clues

We know that certain chemical structures are more likely to affect a particular molecular target site than others. Thus, compounds with structures that are similar to the structures of known phytotoxins or inhibitors of particular plant enzymes or functions may have similar activities. For example, usnic acid (Figure 1), a secondary product from some lichens, is structurally similar to the triketone class of herbicides that inhibit 4-hydroxyphenylpyruvate dioxygenase (HPPD) (e.g., sulcotrione). This led Romagni et al. (2000b) to discover that (−)usnic acid is a better in vitro inhibitor of HPPD than sulcotrione. Natural products that are structural analogs of metabolic intermediates or enzyme cofactors might well be inhibitors of enzymes that use those intermediates or cofactors. For example, AAL-toxin (a toxin from *Altemaria alternata*) (Figure 1) is an analog of the sphingoid base substrates of ceramide synthase, and it is a potent inhibitor of this enzyme (Abbas et al. 1996, 2002). The sugar analog 2,5-anhydro-D-glucitol is phytotoxic (Figure 1) (Tanaka et al. 1996) because of its structural similarity to fructose (Dayan et al. 2002). This protoxin must be phosphorylated by the enzymes hexokinase and phosphofructokinase, yielding the bisphosphorylated analog of fructose-1,6-bisphosphate. Once bioactivated, this phosphorylated sugar analog inhibits fructose-1,6-bisphosphate aldolase.

Using Activity Clues

Many natural compounds have been tested for some type of biological activity other than herbicidal activity. If the mode of action of the activity is known, this information can be used to predict phytotoxicity and mode of action as a herbicide. For example, actinonin (Figure 1) and related compounds were known to be a potent new class of antibiotics with a unique mode of action, inhibition of peptide

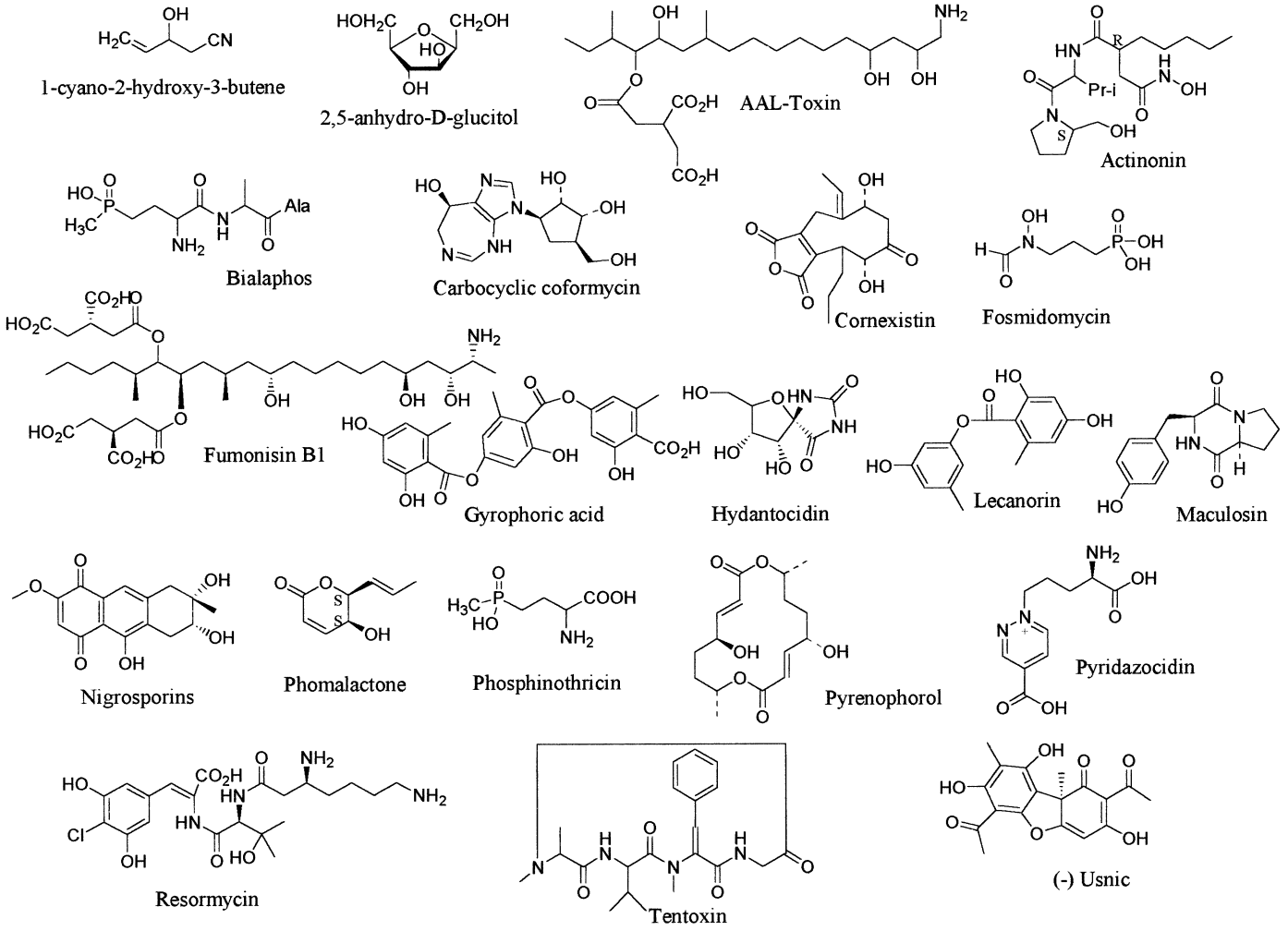

FIGURE 1. Structures of some of the compounds produced by microbes mentioned in the text.

deformylase (Chen et al. 2000). This led Dirk et al. (2001) to find that their phytotoxicity is caused by the same mechanism.

Another example is that of the fumonisins (Figure 1). These compounds were first known to be toxic to animals by inhibiting ceramide synthase (Abbas et al. 1996). Fumonisins and structurally related compounds were found to be extremely phytotoxic by the same mechanism (Abbas et al. 1994).

Yet another example is that of the sesquiterpene lactone, artemisinin (Figure 2), from annual wormwood (*Artemisia annua* L.). This compound was isolated from this common plant because of ethnobotanical clues from Chinese folk medicine regarding its antimalarial properties. It is highly phytotoxic (Duke et al. 1987), but the mechanism of action of artemisinin and several active analogs is unknown (Dayan et al. 1999a). At least one company considered using artemisinin as the basis for development of a new herbicide. Antimalarial compounds might be expected to be herbicidal because *Plasmodium* spp. have a form of plastid with similarities to those of plants (Lang-Unnasch et al. 1998). Another natural product that is toxic to both plants (Zeidler et al. 1998) and *P. falciparum* (Jomaa et al. 1999) is fosmidomycin (Figure 1), an inhibitor of synthesis of all plastid terpenes. Conversely, the synthetic herbicide glyphosate has been shown to be effective against *P. falciparum* (Roberts et al. 1999), and aryloxyphenoxypropionate herbicides are effective against the related parasite *Toxoplasma gondii* (Jelenska et al. 2001).

Discovery of New Compounds

Choosing a Biological Source

There are millions of organisms that have been inadequately studied for the biological properties of the secondary compounds that they produce. This is especially true for soil microbes. There are estimates that less than 1% of soil microbes have been cultured and identified (Felske et al. 1997; Pimm et al. 1995), leaving a potentially huge repository of unknown secondary compounds to be discovered. For the pesticide industry, soil microbes have been the organisms of choice for a source of natural products with potential for herbicides. Two strategies have been utilized: (1) isolation and culture of soil microbes from exotic locations, and (2) manipulation of culture conditions in order to culture previously uncultured organisms. Even when an organism can be cultured, there is no assurance that the culture conditions used will be adequate for the production of every secondary compound that the organism produces in nature.

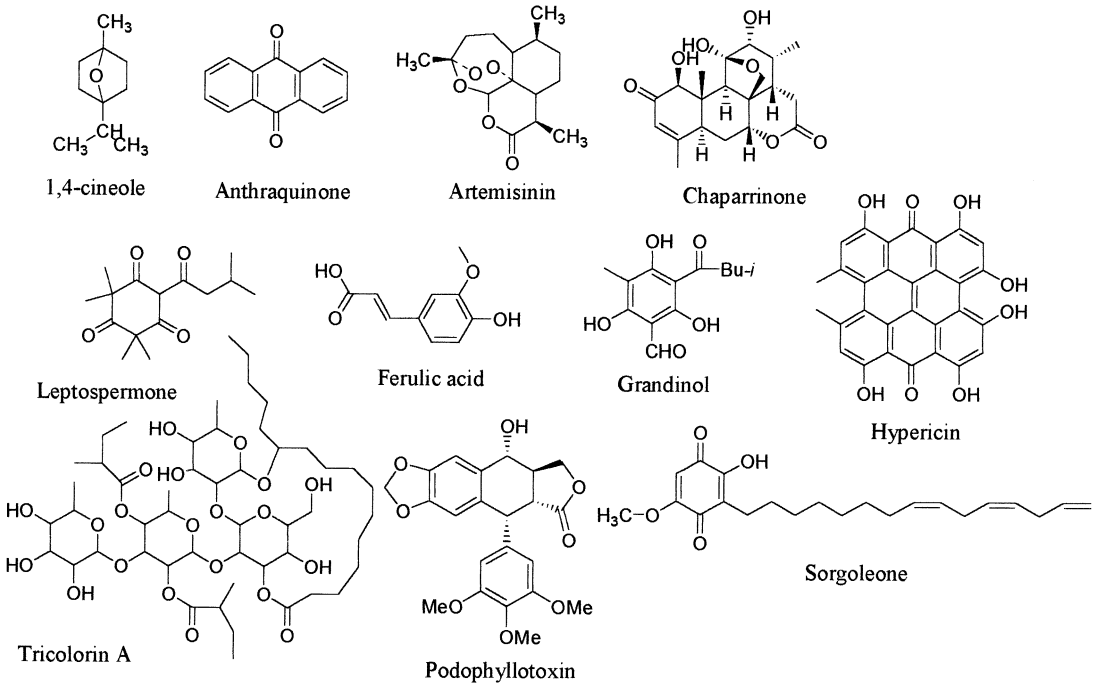

FIGURE 2. Structures of some of the compounds produced by plants mentioned in the text.

Another strategy for phytotoxin discovery with microbes is the chemical ecology strategy. This approach is to examine only those organisms for which there is a reason to believe that a phytotoxin is produced. The most obvious case is that of plant pathogens (Sugawara 2000). For example, a dipeptide phytotoxin, maculosin (Figure 1), was found to be produced by the *Alternaria alternata* that infects spotted knapweed (*Centaurea maculosa* Lam.) (Bobylev et al. 1996). Many, if not most, plant pathogens produce phytotoxins to kill plant cells before they use them as a food source. The greatest difficulty of this approach has been problems in adequately culturing many plant pathogens.

A chemical ecology approach can also be taken in selecting plant species for extraction of phytotoxins. If a plant is known or suspected to be allelopathic, one should expect it to produce phytotoxic allelochemicals (Macias et al. 2001). There are many examples of this from the literature, although relatively few of these studies have adequately fractionated the plant for all phytotoxins. In many cases, bioassay-directed isolation was not carried out, and only water-soluble compounds were isolated.

Plants produce many highly phytotoxic compounds that have no obvious role in plant–plant interactions. For example, artemisinin is produced only in the glandular trichomes of annual wormwood (Duke et al. 1994), yet it is highly phytotoxic, as mentioned earlier. Hypericin (Figure 2), a highly phytotoxic compound, is produced only in certain cells of St. John's wort (*Hypericum perforatum* L.) (Duke et al. 2000a). Both of these compounds are toxic to the producing plant. In the case of artemisinin, the actual function of the compound in nature is unknown, whereas hypericin is an antifeedant. Plants sequester or secrete phytotoxic compounds to avoid autotoxicity (discussed in detail by Duke et al. 2000e). Thus, examination of plants and plant parts with specialized structures for sequestration of secondary compounds is a good strategy for finding phytotoxins.

Bioassay-directed Isolation

Once a biological source is found, it must be fractionated into bioactive components and compounds (Duke et al. 2000b, 2000d, 2000e). Fractionation generally proceeds by initially partitioning extract from the identified biological source between polar and nonpolar solvents. Aliquots are tested for biological activity (e.g., phytotoxicity), and further fractionation is pursued on the fraction where activity is demonstrated. Column chromatography usually follows, and eluates (subfractions) are collected and tested. Chromatographic workup on the bioactive eluate (subfraction) is carried out until a pure compound is obtained. This whole process, which constitutes a bioassay-directed isolation, has resulted in many leads in the discovery of bioactive constituents from medicinal plants (e.g., Choudhary and Atta-ur-Rahman 1997; Pezzuto et al. 1998). Although still of limited practice in the discovery of pesticides, the isolation of an antifeedant compound and nematicidal alkaloids (Choudhary and Atta-ur-Rahman 1997), and phytotoxins from sorghum [*Sorghum bicolor* (L.) Moench] (Rimando et al. 1998), *Leucophyllum frutescens* (Rimando et al. 1999), and *Fusarium solani* (Tanaka et al. 1996) has been accomplished using this approach.

Some important things to consider when undertaking activity-guided natural product isolation are the choice of appropriate bioassay(s), extracting the plant part(s) where the bioactive constituent is most likely to be stored, and testing fractions and subfractions at equal concentrations. Following these guidelines, it was found that an allelopathic rice (*Oryza sativa* L.) cultivar 'Taichung Native 1' contained allelochemicals other than *p*-coumaric acid, a known phytotoxin

TABLE 2. Plant extracts that significantly inhibit germination and growth of the species tested. Data are arranged as follows: edible and medicinal plants are in alphabetical order, and weeds are listed according to their diffusion and economic importance.

Species, family, and biological form[a]	Affected plant(s)	References
Crops		
Asparagus officinalis L.; Liliaceae, Geophyte; asparagus	*Lycopersicon esculentum* Mill., *Asparagus officinalis* L., *Festuca* spp.	Weston 1996; Young 1986
Brassica oleracea L.; Cruciferae, Chamaephyte; cabbage	*Brassica oleracea* L., *Lactuca sativa* L., *Lycopersicon esculentum* Mill.	De Feo et al. 1997; Patrick and Koch 1958, 1963
Canavalia ensiformis (L.) DC.; Leguminosae, Therophyte; jackbean	*Imperata brasiliensis* Trin.	Casini and Olivero 2001; Dinardo et al. 1998
Crambe abyssinica Hochst.; Cruciferae, Therophyte; crambe	*Triticum aestivum* L., *Abutilon theophrasti* Medicus	Vaughn and Berhow 1998
Helianthus annuus L.; Compositae, Theorphyte; sunflower cultivars	*Amaranthus retroflexus* L., *Datura stramonium* L., *Hordeum vulgare* L., *Lactuca sativa* L., *Lepidium sativum* L., *Lycopersicon esculentum* Mill., *Triticum aestivum* L., *Trifolium* sp.	Barberi et al. 1998; Hall et al. 1982; Hilton 1979; Macias et al. 1996, 1999; Narwal et al. 1999
Hordeum vulgare L.; Gramineae, Therophyte; barley	*Sinapis alba* L.	Kati and Froud-Williams 1999
Jugians nigra L.; Juglandaceae, Phanerophyte; black walnut	*Lycopersicon esculentum* Mill.	Rice 1984; Willis 2000
Olea europaea L.; Oleaceae, Phanerophyte; olive oil mill wasterwater	*Amaranthus retroflexus* L., *Chenopodium album* L., *Portulaca oleracea* L., *Raphanus sativus* L.	Aliotta et al. 2000
Oryza sativa L.; Gramineae, Therophyte; rice accessions	*Lactuca sativa* L., *Oryza sativa* L., *Echinochloa crus-galli* (L.) Beauv.	Chou and Lin 1976; Lin et al. 2000; Narwal 2000; Olofsdotter et al. 1999
Sorghum bicolor (L.) Moench; Gramineae, Therophyte; sorghum	*Festuca* spp.	Hall et al. 1982; Hilton 1979; Macias et al. 1996; Weston et al. 1999
Secale cereale L.; Gramineae, Therophyte; rye	*Chenopodium album* L.	Chou and Patrick 1976; Barnes et al. 1986
Triticum aestivum; Gramineae, Therophyte; wheat accessions	Several weeds	Narwal 2000
Ruta graveolens L.; Rutaceae, Phanerophyte; rue	*Amaranthus retroflexus L., Chenopodium album* L., *Portulaca oleracea* L., *Raphanus sativus* L.	Aliotta and Cafiero 1999; Aliotta et al. 2000
Zea mays L.; Gramineae, Therophyte; maize	Several weeds	Bingamen and Christians 1995; Christians 1993; Gough and Caristrom 1999
Weeds		
Cyperus rotundus L.; Cyperaceae, Geophyte; purple nutsedge	*Allium cepa* L., *Brassica nigra* (L.) Koch, *Brassica oleracea* L., *Cucumis sativus* L., *Daucus carota* L., *Fragaria* sp. pl., *Gossypium* sp., *Glycine max* (L.) Merr., *Hordeum vulgare* L., *Lycopersicon esculentum* Mill., *Oryza sativa* L., *Raphanus sativus* L., *Sorghum bicolor* (L.) Moench.	Friedman and Horowitz 1971; Lucena and Doll 1976; Singh 1968; Velu and Aruna 1996; Wibiwo 1996.
Cynodon dactylon (L.) Pers.; Gramineae, Geophyte; Bermuda grass	*Hordeum vulgare* L., *Glycine max* (L.) Merr.	Horowitz and Friedman 1971; Velu and Aruna 1996
Echinochloa crus-galli (L.) Beauv.; Gramineae, Therophyte; barnyard grass	*Triticum durum* L., *Glycine max* (L.) Merr., *Oryza sativa* L.	Dilday et al. 1998; Gressel and Holm 1964
Eleusine indica (L.) Gaertner; Gramineae, Therophyte; goosegrass	*Phaseolus vulgaris* L., *Sorghum bicolor* (L.) Moench, *Zea mays* L.	Altieri and Doll 1978
Sorghum halepense (L.) Pers.; Gramineae. Geophyte; johnson grass	*Coronilla varia* L., *Glycine max* (L.) Merr., *Gossypium* sp., *Hordeum vulgare* L.	Abdul-Wahab and Rice 1967; Bieber and Hoveland 1968; Horowitz and Friedman, 1971
Imperata cylindrica (L.) Beauv.; Gramineae, Geophyte; cogon grass	*Cucumis sativus* L., *Lycopersicon esculentum* Mill., *Oryza sativa* L., *Sorghum bicolor* (L.) Moench, *Zea mays* L.	Abdul-Wahab and Al-Naib 1972; Eussen 1978; Eussen and Soerjani 1978

Table 2. Continued.

Species, family, and biological form[a]	Affected plant(s)	References
Portulaca oleracea L.; Portulacaceae, Therophyte; purslane	*Medicago sativa* L., Lycopersicon esculentum Mill., *Triticum durum* L.	Le Tourmeau et al. 1956
Chenopodium album L.; Chenopodiaceae, Therophyte; lambsquarter	*Beta vulgaris* L., *Brassica oleracea* L., *Triticum aestivum* L., *Zea mays* L.	Kossanel et al. 1977; Williams 1964
Digitaria sanguinalis (L.) Scop.; Gramineae, Therophyte; crabgrass	*Coronilla varia* L., *Harachis hypogea* L., *Gossypium* sp., Nitrificant bacteria	Gressel and Holm 1964; parenti and Rice 1969; Rice 1964
Convolvulus arvensis; Convolvulaceae, Hemicryptophyte; field bindweed	*Triticum aestivum* L. cv. Pavon	Alam et al. 1998
Avena fatua L.; Gramineae, Therophyte; wild oat	*Triticum aestivum* L., *Linum* sp., *Hordeum vulgare* L.	Schumacher et al. 1982; Tinnin and Muller 1971
Amaranthus retroflexus L.; Amaranthaceae, Therophyte; redroot pigweed	*Triticum durum* L., *Glycine max* (L.) Merr.	Bhowmik and Doll 1979; Qasem 1995

[a] Chamaephyte: any perennial plant whose winter buds are within 25 cm of the soil surface. Geophyte: a perennial plant that is deeply embedded in the soil substrate. Hemicryptophyte: a plant having buds at the soil surface and protected by scales, snow, or litter. Phanerophyte: a perennial tree or shrub with dormant buds borne on aerial shoots. Therophyte: an annual plant whose seed is the only overwintering structure.

found in the leaves and stems of rice (Chou et al. 1981). When tested at the same concentrations, the fraction containing *p*-coumaric acid, as well as a pure sample of *p*-coumaric acid, was not active against barnyardgrass [*Echinochloa crus-galli* (L.) Beauv.]. Phytotoxicity was detected in other fractions (Rimando et al. 2001).

Bioactivity-guided isolation is becoming an automated procedure where modern instrumentation in tandem is constructed to allow splitting of eluents, as peaks are detected, from extracts injected into a high-performance liquid chromatograph, a portion of which is collected into bioassay plates (e.g., 96-well plates), while another portion is diverted for structural analysis to a mass (Constant and Beecher 1995) or a nuclear magnetic resonance (NMR) spectrometer (Lindon et al. 1996). Fully automated analytical instrumentation, coupled with autosamplers for collecting fractions for bioassay, greatly reduces the time and effort put into the isolation of known compounds, while also maximizing the chance to identify new chemical entities with a specific biological activity (Hook et al. 1997). The power of a fully automated and integrated instrumentation has been demonstrated in the identification of 5-nitropyridone and other metabolites from corn (Bailey et al. 2000). Discovery of natural herbicides will be greatly facilitated using fully automated tandem instrumentations, such as liquid chromatography–mass spectrometry (LC/MS) and LC/MS/NMR.

Crude Extracts

There are a number of different ways to obtain collections of plants for novel drugs and allelochemical screening. These range from random screening to informed selection based on taxonomic, chemical, or ethnobotanical data, or any combination of these. As about three-quarters of the biologically active plant-derived compounds presently in use worldwide have been discovered through follow-up research to verify the authenticity of data from folk and ethnomedicinal uses (Farnsworth 1990), it is reasonable to conduct ethnobotanically directed research in order to optimize the search for novel biologically active principles.

Since the emergence of agriculture and after a long period of adaptive coevolution between man and plants (Harlan 1992), an empirical body of knowledge has accumulated concerning the manipulation of ecosystems without the use of synthetic herbicides. Greek and Roman agronomists such as Theophrastus, Cato the Elder, Varro, Virgil, Columella, and Pliny the Elder wrote treatises on agriculture dealing with the methods of good crop husbandry used to minimize weed interference with crops, such as hand weeding, crop rotation, mechanical, tillage, burning, and mulching. Their insights came before any understanding of allelopathy or its mechanisms. Successively, farmers observed many allelopathy-related phenomena, for instance, that tomatoes (*Lycopersicon esculentum* L.) grow poorly under black walnut trees (*Juglans nigrum* L.), and *sorghum* spp. plant residues and certain varieties of crop plants inhibit the growth of many weeds. We now know that many such relationships involve allelochemicals produced by plants (Waller 1987). Crude preparations of many plants significantly inhibit the germination and growth of species (Table 2). Theoretically, such preparations could be used as natural herbicides, although very little research has been conducted to exploit this approach. A more fruitful approach has been to use waste products from plants that are processed for food or oil.

For example, corn gluten meal, a by-product of the wet-milling process, is being used for preemergence weed management and fertilization (Bingamen and Christians 1995; Christians 1993; Gough and Carlstrom 1999). Corn gluten hydrolysate, produced by the action of a bacterial proteinase, is more active than the gluten meal as a herbicide (Liu and Christians 1994a). The hydrolysate is active on both grasses and broadleaf weeds (Liu and Christians 1997). The hydrolysate contains five phytotoxic dipeptides, with alanylalanine being the most active (Liu and Christians 1994b). Numerous physiological effects of alanylalanine have been reported

(Unruh et al. 1997a, 1997b), but the molecular target site is unknown. Later, a more active pentapeptide (leu-ser-pro-ala-gln) was isolated from corn gluten hydrolysate (Liu and Christians 1996), but very little information is available on it.

Another seed meal waste product that could be used for weed management is that of crambe (*Crambe abyssinica* Hochst. ex R. E. Fries), a crop grown for oil and erucic acid (Vaughn and Berhow 1998). A major phytotoxin in this material is 1-cyano-2-hydroxy-3-butene (Figure 1). Seed meals from phytotoxic, glucosinolate-containing plants have also been shown to be potentially useful for weed management as a soil amendment (Vaughn et al. 1996).

Crude preparations of natural products must originate from crops or other organisms. There are many problematic issues with such products, such as supply, cost, and efficacy. The supply problem is likely to preclude widespread use in agronomic crops; however, certain niche markets could be ideal for this type of product.

Pure Compounds

Microbial Products

Products of Plant Pathogens

Plant pathogens produce a myriad of phytotoxins that are apparently useful in weakening the plant in the infection process. Most of these compounds are not host selective, even though the producing pathogen might infect only one or a limited number of host species. However, some of them are reported to be highly active against only one species or even certain genotypes of that species. Unless the host is a huge weed problem, there is little interest in herbicides that are extremely selective.

However, the literature on host-selective toxins is suspect from a herbicide standpoint. Plant pathologists have not always adequately evaluated these compounds for herbicidal activity. For example, AAL-toxin has been claimed to be a host-selective phytotoxin, affecting only certain tomato varieties (Abbas et al. 1995), yet it is one of the most generally phytotoxic natural products evaluated for herbicidal activity (Abbas et al. 1996). Other somewhat host-selective phytotoxins for weeds have been proposed, but not adequately tested. These include pyrenophorol (Figure 1) for wild oat (*Avena fatua* L.) control (Kastanias and Chrysayi-Tokousbalides 2000) and maculosin (Figure 1) for spotted knapweed (Bobylev et al. 1996).

Space limitations do not permit mentioning many of the other phytotoxins from plant pathogens that have been described (Duke et al. 1996).

Other Microbial Compounds

Some of the more potent natural phytotoxins have come from nonpathogenic microbes. The bacterial phytotoxins of this type are reviewed by Barazani and Friedman (2001). We shall provide a few examples, with emphasis on those that have been most successful or spurred the most interest.

The actinomycete-produced compound, actinonin (also known as butanediamide) (Figure 1), is a potent inhibitor of peptide deformylase (Chen et al. 2000), an important enzyme of bacteria and chloroplasts (Dirk et al. 2001). Peptide deformylase is necessary for the posttranslational processing of some chloroplast genome–encoded proteins. This is a site of action unique to plants and bacteria that has potential for the development of a new herbicide class. Although it is not extremely active on whole plants, it is highly active ($I_{50} < 100$ nM) on one out of two chloroplast peptide deformylases (Dirk et al. 2001).

Bialaphos (Figure 1) and phosphinothricin (Figure 1), both *Streptomyces* spp. products, are successful herbicides (Lydon and Duke 1999). Bialaphos is manufactured as a fermentation product and sold in a limited market in Japan. It is a proherbicide, requiring metabolic conversion to phosphinothricin in the target plant for herbicidal activity. Phosphinothricin is synthetically produced as glufosinate. It is the only herbicide that inhibits glutamine synthetase. It is nonselective, and many crops have been engineered to be resistant to it by inserting a transgene that encodes a detoxification gene from the producing *Streptomyces*. Phosphinothricin (glufosinate) is the biggest success story for a natural product-based herbicide. It is relatively inexpensive, toxicologically and environmentally safe, and efficacious on a wide range of target weeds. Thus, with herbicide-resistant crops, it has many of the same advantages of glyphosate in glyphosate-resistant crops.

Hydantocidin (Figure 1) is an *S. hygroscopicus* product with good herbicidal activity (reviewed by Duke et al. 1996, 2000b). It is a proherbicide that must be phosphorylated by the target plant to be an inhibitor of adeynloscuccinate synthetase. Many analogs have been patented, but none of them have been marketed. Its nucleic acid synthesis site of action may be a cause for toxicological concern.

Pyridazocidin (Figure 1) is another *Streptomyces* sp. phytotoxin with an interesting mode of action (Gerwick et al. 1997). It is only a weak phytotoxin, but it is the only natural phytotoxin known to act by the same mechanism as paraquat, by accepting electrons from photosystem I and transferring them to molecular oxygen to generate a superoxide radical.

Cornexistin (Figure 1) and hydrocornexistin are products of a nonpathogenic fungus *Paecilomyces variotii*. Both of these compounds are very phytotoxic and have been patented as herbicides (Fields et al. 1996). Cornexistin has a unique molecular target site, aspartate amino transferase (Amagasa et al. 1994). The two compounds have different selectivity on crops and weeds.

New and interesting phytotoxins from microbes are being discovered at a high rate. For example, phomalactone (Figure 1) was recently found to cause rapid electrolyte leakage of plant plasma membranes, leading to plant death (Fukushima et al. 1998). Resormycin (Figure 1) (Igarashi et al. 1997) and the nigrosporins (Figure 1) (Tanaka et al. 1997) are interesting new phytotoxins with activity against both grasses and broadleaf weeds.

Lichens, a symbiotic relationship between algae and fungi, produce several different secondary compounds. The lichen is not a microbe, but the algae and fungi making it up could be considered microbes. Many lichen species are structurally unique, with ca. 50 to 60 of the 630 known lichen metabolites occurring in other fungi or higher plants. Most of the common lichen secondary metabolites are derived from the polyketide biosynthetic pathway (also called acetyl-polymalonyl pathway), with a few originating from the shikimate and mevalonate biosynthetic pathways. The

majority of lichen secondary metabolites originate from the fungal partner and are produced extracellularly when the organisms are in their obligate symbiotic association. Under specific conditions, where the symbionts have been artificially separated in the laboratory, other secondary compounds are produced; however, these are different from those produced in the symbiosis. Lichen secondary products may comprise up to 20% of the thallus dry weight, although 5 to 10% is more common. The unusual chemicals present in lichen and their biological activities can potentially be used to develop novel herbicide management tools.

The phytotoxic effect of certain lichen metabolites may deter the growth of other lichen populations as well as that of seedlings competing for a particular ecological niche. Several lichen species are found in the canopy and compete for space with ferns, fern allies, mosses, small seedlings, and other lichen species. Because lichens generally grow much slower than most of the competing species, they must have several defense strategies.

There is generally little information in the literature concerning the phytotoxic activity of specific lichen products. Most information concerns the antimicrobial or human health benefits of lichen secondary products. There are some studies, however, that document the specific activity of these compounds. The depsides barbatic acid and lecanoric acid (Figure 1), and the tridepside gyrophoric acid (Figure 1) act like PSII-inhibiting herbicides (e.g., atrazine, diuron) by interrupting photosynthetic electron transport in isolated chloroplasts (Endo et al. 1994; Rojas et al. 2000).

As mentioned previously, one interesting aspect of the allelopathic potential of lichens is related to the ability of (−) usnic acid to inhibit carotenoid biosynthesis through the enzyme HPPD (Romagni et al. 2000b). The in vitro activity of usnic acid is superior to that of other synthetic inhibitors of this herbicide target site. The ability of usnic acid to inhibit HPPD may contribute to an allelopathic effect. Synthetic inhibitors of this enzyme, e.g., sulcotrione and mesotrione, are currently being used as herbicides.

In another study, Lasceve and Gaugain (1990) documented the effects of usnic acid on sunflower (*Helianthus annuus* L.) and corn plants. There was a 40% decline in transpiration as well as dwarfism and root malformation. The actual mode of action was not determined; however, the concentration of usnic acid was 500 μM, and this might have caused secondary toxicity effects.

Abo-Khatwa et al. (1996) also studied three lichen acids, atranorin, usnic, and vulpinic acid, but found that they had characteristic effects similar to 2,4-dinitrophenol, an uncoupler of oxidative phosphorylation. The actual mode of action was not determined.

Several analogs of lichen-derived anthraquinones have strong herbicidal activity. Certain analogs of emodin, an anthraquinone found in nonlichen as well as lichenicolous fungi, are highly specific for grasses, causing malformation and bleaching in early seedlings. Other analogs of rhodocladonic acid cause root malformations in both dicot and monocot seedlings. Several of these completely inhibit germination.

Most of the lichen compounds are chemically simple, making them relatively easy to synthesize in the laboratory. Doing so would provide large amounts of material without harming the ecosystems. In addition, many of these compounds can be used as lead structures based on their particular mechanism of action and can then be optimized in the laboratory to fit specific applications.

Phytochemicals

Plants produce a very large number of interesting phytotoxins with potential use as herbicides. For example, leptospermone (Figure 2) is an allelochemical from which the triketone class of herbicides was developed (Mitchell et al. 2001). This is perhaps the most successful development of a commercial herbicide from a phytochemical.

Monoterpene cineoles are natural products commonly found in the essential oils from aromatic plants such as *Laurus nobilis* L., *Salvia* spp., *Eucalyptus* spp., and *Artemisia* spp. Many volatile monoterpenes are phytotoxic. Of those compounds, 1,8-cineole has been identified as one of the most potent allelochemicals released by *Artemisia* spp. 1,4-Cineole (Figure 2) is also common but is usually present in much lower concentrations. It has been recently reported that 1,4-cineole, a structural analog of the herbicide cinmethylin, was a potent inhibitor of asparagine synthetase (Romagni et al. 2000a).

Quassinoids are phytotoxic compounds produced by several plant species of the Simaroubaceae family (Heisey 1990; Lin et al. 1995). Chapparrinone (Figure 2) and its derivatives are active on plants at 1- to 5-μM concentrations. Chaparrinone-type quassinoids have broad weed spectrum activity when applied either as preemergence or postemergence herbicide and can provide 100% control of green foxtail [*Setaria viridis* (L.) Beauv.] and sicklepod [*Senna obtusifolia* (L.) Irwin & Barneby] at rates of 0.125 kg ha^{-1}. Quassinoids cause strong inhibition of the latter stages of mitosis but do not affect prophase, suggesting that these compounds do not prevent induction of the cell cycle. The primary site of action appears to be the inhibition of reduced nicotinamide adenine dinucleotide oxidase (Morré et al. 1998), and the presence of an oxymethylene bridge between C8 and C11 of the quassinoid backbone was required for the herbicidal activity (Dayan et al. 1999c).

There are many plant-derived compounds that inhibit mitosis of plants (Vaughan and Vaughn 1988). For example, podophyllotoxin (Figure 2) is an aryltetralin lignan extracted from the leaves of mayapple (*Podophyllum peltatum* L.) and has been studied extensively because of its ability to inhibit microtubule assembly in mammalian cells and its strong antiviral activity (Imbert 1998). Numerous semisynthetic derivatives of podophyllotoxin, such as etoposide and tenoposide, having inhibitory activity against DNA-topoisomerase II, have been developed as effective antineoplastic drugs (Canel et al. 2000). When tested for phytotoxicity, this compound was more active against the monocotyledonous Italian ryegrass (*Lolium multiflorum* Lam.) than against the dicotyledonous lettuce (*Lactuca sativa* L.) species tested (Oliva et al. 2002). Moreover, the inhibition of root growth observed in the bioassays suggested that podophyllotoxin affected either cell division or cell elongation. Its inhibitory effect on the different mitotic phases, and especially on prophase, indicates that this compound affects mitosis. In addition, abnormal mitotic stages observed in root cells exposed to 100 μM podophyllotoxin suggested that this compound acted as a natural mitotic disrupter (Vaughan and Vaughn 1990). Effects were noted only on the cell division stages past prometaphase. At this stage, the normal spindle

microtubular organizing center seemed to be affected by the tested compound, so that the microtubules were oriented toward multiple poles where the chromatids appeared in "star anaphase" figures. This display is similar to that found when the herbicides terbutol, sindone B, pronamide, dithiopyr, and some carbamate herbicides were tested at low concentrations (0.1 to 30 μM) (Hoffman and Vaughn 1994; Lehnen and Vaughn 1992; Lehnen et al. 1990). Although the precise molecular mechanism of action of this compound remains to be identified in plants, a primary effect is the alteration of the formation of the spindle microtubular organization centers, resulting in the formation of multiple spindle poles, leading to an asymmetrical convergence of the chromatids.

Sorgoleone (Figure 2) is an allelochemical exuded in oily droplets from the roots of sorghum (Netzly and Butler 1986). The concentration of sorgoleone in soils growing sorghum can reach 10^{-4} to 10^{-5} M (Netzly et al. 1988) and lead to suppression of weed growth (Forney and Foy 1985). This potent phytotoxin represses the growth of large crabgrass seedlings [*Digitaria sanguinalis* (L.) Scop.] with a GR_{50} of 10 μM for shoot and root growth (Nimbal et al. 1996). Inhibition of shoot and root growth of velvetleaf (*Abutilon theophrasti* Medikus) and barnyardgrass have also been observed at concentrations from 10 to 200 μM. Sorgoleone inhibits photosynthetic electron transport in thylakoids by competing for the plastiquinone binding site on photosystem II. This compound has the same level of inhibitory activity of photosynthetic electron transport as diuron, 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU), with an I_{50} of 100 and 120 nM, respectively (Gonzalez et al. 1997; Nimbal et al. 1996).

Multicolored morningglory (*Ipomoea tricolor* Cav.) is used in traditional agriculture in Mexico for weed management. It contains resin glycosides of which tricolorin A (Figure 2) is the principal constituent (Pereda-Miranda et al. 1993). This compound is highly phytotoxic and a potent inhibitor of plasma membrane adenosine triphosphatase (Calera et al. 1995).

Other Phytochemicals

Grandinol (Figure 2) is a phloroglucinol-related compound that inhibits germination, photosynthesis, transpiration, and stomatal opening (Yoneyama et al. 1996).

Natural Compounds from Other Sources

Secondary products with many kinds of biological activity are produced by all types of marine organisms and animals. For example, certain ants apparently produce herbicidal compounds to kill the vegetation surrounding their habitat (Renner and Ricklefs 1998). Relatively little effort has been made to examine such compounds for their potential as herbicides.

Natural Compounds for Use as Algicides—A Niche Market

Aquaculture is one of the fastest growing areas of agriculture in the world, and in the United States catfish is the largest and fastest growing segment of aquaculture. Off-flavors, which render cultured catfish unpalatable and thereby unmarketable, cause large economic losses every year. Certain species of cyanobacteria (blue-green algae) that grow in catfish aquaculture ponds produce compounds that cause objectionable flavors. The musty flavor of 2-methylisoborneol (MIB) is most commonly found in the flesh of cultured catfish raised in Mississippi, which provides over half of the world's supply of farm-raised channel catfish (*Ictalurus punctatus*). The cyanobacterium *Oscillatoria perornata* (Skuja) has been identified as the leading cause of the musty off-flavor in catfish produced in west Mississippi (van der Ploeg et al. 1992).

The only compounds approved by the United States Environmental Protection Agency (USEPA) for application as an algicide in catfish production ponds in Mississippi are diuron and copper-based products, such as chelated-copper products and copper sulfate. Currently, the USEPA must grant catfish farmers an emergency exemption for every year that it is to be used, and therefore there is no guarantee of renewal each year. The algicides currently used are not selective and kill other groups of phytoplankton, such as green algae (Chlorophyta) (Schrader et al. 1998a). Green algae are the preferred type of phytoplankton, compared with cyanobacteria, in catfish production (Paerl and Tucker 1995). Additional undesirable attributes of the use of synthetic compounds as algicides in aquaculture ponds include environmental safety issues and the public's negative perception of the use of synthetic chemicals in food-production ponds.

The discovery of environmentally safe natural compounds that are selectively toxic toward odor-producing species of cyanobacteria would greatly benefit commercial catfish producers. There are few studies concerning the use of natural compounds as selective algicides in catfish ponds. The earliest reported studies involve the discovery of several oxygenated fatty acids (allelochemicals produced by the aquatic plant *Eleocharis microcarpa*) that inhibited the growth of cyanobacteria found in catfish ponds (Van Aller and Pessoney 1982; Van Aller et al. 1985). Potassium ricinoleate was determined to be structurally similar to the active fatty acids, and the commercial algicide Solricin 135® (Caschem, Inc., Bayonne, NJ) contains potassium ricinoleate as the active ingredient. However, Tucker and Lloyd (1987) found that potassium ricinoleate was ineffective in controlling undesirable species of cyanobacteria in efficacy studies conducted in catfish ponds. Another more recent study has evaluated the use of decomposing barley (*Hordeum vulgare* L.) straw to control cyanobacteria in catfish ponds (Wills et al. 1999). Welch et al. (1990) were among the first to report the reduction of filamentous algae because of the presence of decomposing barley straw placed in a canal in the U.K. One possible mechanism for algal inhibition may be the result of the release of antialgal compounds from the decomposing barley straw (Pillinger et al. 1994). Studies by Wills et al. (1999) have found that decomposing barley straw does not prevent musty off-flavor in cultured catfish.

Recent discoveries by Schrader and Harries (2001) and Schrader et al. (1998b) have identified several promising natural compounds produced by certain plants that are selectively toxic toward *O. perornata*. One of these compounds, ferulic acid (Figure 2), was pond-tested, and numbers of *O. perornata* were not significantly reduced by ferulic acid application (Schrader et al. 2000b). These unfavorable results were attributed to the rapid dissipation of ferulic acid

from the water column. This study provides an example of a potential concern for using natural compounds as algicides in highly eutrophic catfish aquaculture ponds. In such an ecosystem certain toxic natural compounds may undergo rapid dissipation, degradation, or transformation, thereby limiting sufficient contact with or uptake by the target microbe to provide an effective means for elimination of the noxious organism.

Anthraquinone (Figure 2) is another promising natural compound identified as a selective algicide during laboratory screening (Schrader et al. 1998b). Anthraquinone appears to inhibit electron transfer in photosystem II in *O. perornata* (Schrader et al. 2000a). Subsequent efficacy testing of anthraquinone found that it was ineffective in reducing the numbers of *O. perornata* or the levels of MIB in pond water when applied in a solution of ethanol or as an oil emulsion (Schrader, unpublished data). Anthraquinone ineffectiveness as a selective algicide in pond tests was attributed to its lack of solubility in water. This problem highlights another consideration in using a natural compound as a selective algicide in that the compound must be in a form or applied in a way that maintains it in the water in an active (toxic) state so that it can effectively enter the target organism.

There are also considerations in selecting natural compound leads for subsequent development as commercial algicides. For example, the cost to the catfish farmer must be considered. A compound must be effective in controlling the undesirable cyanobacterial species at a low concentration ($\mu g\ L^{-1}$ range), and the cost of synthesis at the industrial-scale level will affect the cost to the farmer. Also, there are several environmental safety concerns that must be addressed, including persistence of the natural compound in the catfish pond water and sediment, potential breakdown products of the compound, its toxicity toward nontarget organisms (e.g., catfish), and its potential accumulation in and metabolism by catfish.

Limitations and Future Research

We have described the benefits and successes of using natural products as herbicides or for herbicide discovery. So, why is there not more interest in this approach? There are a number of problems associated with natural products that have deterred a stronger interest.

First, many natural products are too expensive to be seriously considered for use as agrochemicals because of their structural complexity. For example, the cyclic tetrapeptide tentoxin (Figure 1) is an excellent herbicide but is very expensive. Considerable structure–activity research to find a simpler, less expensive molecule with similar activity (e.g., Bland et al. 1993; Edwards et al. 1988) was unsuccessful. Conversion of the molecule to another complex structure yields isotentoxin, a compound with a different mode of action (Liebermann et al. 1996). Another example is that of carbocylic coformycin (Pillmoor 1998) (Figure 1). This compound with a unique mode of action (Table 1) could not be synthesized economically. Even close analogs had little or no herbicidal activity. In cases where the function of the compound in nature is that of a phytotoxin, the structure may have been optimized by nature. In such cases, if the structure is complex, attempts to generate a low-cost molecule may be unsuccessful.

The popular media bombard the public with the medieval herbalist concept that everything in nature is healthy, but many of the most toxic compounds known to humans are natural (e.g., aflatoxin, fumonisins, ricin). Some highly phytotoxic natural products are also very toxic to mammals. For example, AAL-toxin is quite toxic to mammalian cells (Abbas et al. 1996). This aspect of some natural phytotoxins has terminated interest in them for the development for weed management. Nevertheless, from an environmental toxicology standpoint, the relatively short half-life of most natural compounds in the field is desirable. Regulation of natural product-based pesticides varies from one country to another (Neale 2000). According to current regulations, the USEPA may require the same scrutiny for a natural product as for a synthetic pesticide.

The intellectual property rights associated with rare organisms from exotic places have become quite complicated. Developing countries, especially, have felt that their biological resources have been exploited by institutions from the developed world for the discovery of pharmaceuticals. This has resulted in these countries passing laws to retain some level of ownership of compounds discovered from organisms taken from within their borders (ten Kate and Laird 1999). In some cases, this has discouraged discovery efforts that use the biological diversity of certain places.

Until recently, the cost of compound isolation and structure elucidation was very high. This problem, coupled with the rediscovery of known compounds (e.g., Ayer et al. 1989; Heisey et al. 1988), was discouraging. Modern tandem instrumentation, such as LC/MS/MS and LC/NMR, and automation of determination of compounds within a complex extract (Hook et al. 1997) has greatly reduced the time and effort needed to identify isolated compounds. Precise profiling of known compounds in standard bioassays and use of this information to eliminate costly purification and structure elucidation of known compounds has been a strategy to reduce cost. However, if standards are set too high, this approach will result in the loss of some new compounds with similar activity to known compounds. Tandem analytical instrumentation should eliminate this choice, allowing rapid and inexpensive determination of whether the suspected known compound is in the fraction. If not, bioassay-directed isolation can proceed.

The relatively short environmental half-life of natural products is good from an environmental toxicology standpoint, but a herbicide must persist sufficiently long to have the desired effect. We have found, in some cases, that some natural herbicides do not persist long enough to be effective (e.g., Schrader et al. 2000b).

Synthetic chemistry is the dominant approach to herbicide discovery. The recent high level of investment in combinatorial chemical synthesis and high throughput screening has reinforced this approach. Pillmoor (1998) stated in his discussion of natural product approaches that "unless the commitment is there to invest in this work, then the value of undertaking natural product research in the first place is somewhat questionable." We believe that modern instrumentation and improved methods should increase interest in natural product-based herbicide discovery research.

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