Neem and Other Botanical Insecticides: Barriers to Commercialization[1]

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In spite of the wide recognition that many plants possess insecticidal properties, only a handful of pest control products directly obtained from plants, *i.e.*, botanical insecticides, are in use in developed countries. The demonstrated efficacy of the botanical neem (based on seed kernel extracts of *Azadirachta indica*), and its recent approval for use in the United States, has stimulated research and development of other botanical insecticides. However, the commercialization of new botanical insecticides can be hindered by a number of issues. The principal barriers to commercialization of new botanicals are (i) scarcity of the natural resource; (ii) standardization and quality control; and (iii) registration. These issues are no problem (i) or considerably less of a problem (ii, iii) with conventional insecticides. In this review I discuss these issues and suggest how the problems may be overcome in the future.
KEY WORDS: Botanical insecticides; neem; azadirachtin; pyrethrum; pesticide registration.

INTRODUCTION

Prior to the discovery of the organochlorine and organophosphate insecticides in the late 1930s and early 1940s, botanical insecticides were important products for pest management in industrialized countries. The importation of plant material or derivatives thereof for use as insecticides represented a considerable enterprise: for example, over 6700 (U.S.) tons of *Derris elliptica* roots was imported into the USA from southeast Asia in 1947, but this decreased to 1500 tons in 1963 (16). This reflects the extent to which botanicals have been displaced by synthetic insecticides. The trend continues: in 1990, imports of pyrethrum in the USA totaled just over 350 tons (7). Also, some botanical insecticides that had enjoyed use in North America and western Europe have lost their regulatory status as approved products. These include nicotine (from *Nicotiana tabacum*), quassin (from *Quassia amara* and *Picrasma excelsa*), and ryania (from *Ryania speciosa*). As a consequence, the only botanicals in wide use in North America and Europe are pyrethrum (from *Chrysanthemum cinerariaefolium*) and rotenone (from *Derris* spp. and *Lonchocarpus* spp.), although neem (*Azadirachta indica* A. Juss.) is approved for use in the USA and regulatory approval is pending in Canada and Germany. At best, botanical insecticides presently constitute 1% of the world insecticide market, but annual sales growth in the range of 10–15% is entirely possible. The impact of botanicals will perhaps be most noticeable in the home-and-garden sector, where they might conceivably achieve as much as a 25% market share within 5 years.

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From the academic point of view, plants represent a vast storehouse of potentially useful natural products, and indeed, many laboratories worldwide have screened thousands of species of higher plants not only in search of pharmaceuticals, but also for pest control products (for examples, see refs. 2, 15). These studies have pointed to numerous plant species possessing potential pest-controlling properties under laboratory conditions, but the step from the laboratory to the field eliminates many contenders, even when judged only on their efficacy against pests under realistic field conditions. Unfortunately, efficacy against pests is only one of a number of important criteria that need be met for a plant extract or derivative to move successfully toward commercialization and use (9).

Apart from efficacy and spectrum-of-action, biological criteria include favorable toxicology and minimal environmental impact (*i.e.*, vertebrate selectivity; selectivity favoring natural enemies and pollinators; rapid environmental degradation). Neem insecticides meet these criteria admirably, yet the commercialization of neem for use in North America and Europe has taken many years and the costs have run into millions of US dollars. Obviously, it is not enough to have an efficacious product that is relatively safe to the user and the environment – there are other considerations that must be satisfied. I argue that these 'other' considerations constitute barriers to the commercialization of other botanical insecticides. They include: (i) the relative scarcity or availability of the natural resource; (ii) standardization of extracts and quality control, based on active ingredients; and (iii) special problems in regulatory approval of botanicals. These issues are no problem (i) or constitute considerably less of a problem (ii, iii) with conventional pesticides.

RESOURCE AVAILABILITY

There is little point to investing millions of dollars to develop a new pesticide based on a plant unless there is reasonable assurance that the starting material can be obtained in sufficient quantities to meet market demand, and on a consistent basis. Unless the plant in question is extremely abundant in nature, it will be necessary to cultivate it to obtain sufficient biomass for extraction. As examples, both pyrethrum and rotenone are obtained in quantity through cultivation. At present, neem seeds are harvested in India from among the estimated 25 million existing trees. However, many of those trees have been intentionally planted in towns and villages, and the harvest of seed to provide oil for the soap industry was well established in India prior to the development of commercial insecticides from neem. Plantations of neem trees have been established in such diverse tropical countries as Australia, Brazil and Kenya, specifically to provide the biomass for the production of natural insecticides and pharmaceutical products.

One of the best sources of biomass for production of botanical insecticides is the seeds produced as waste products of the fruit juice industry. In the United States, thousands of tons of grapefruit seeds are generated annually by the citrus industry, from which an estimated 300 tons of limonoids could be obtained on an annual basis (12). The major limonoid in citrus seeds, limonin, is a potent antifeedant to the Colorado potato beetle, the key pest of cultivated potato in North America, Europe and Russia (1). In southeast Asia, juice is prepared from fruit of the sour sop (*Annona muricata*); an estimated 8,500 tons of fruit are produced annually in the Philippines alone (13). The seeds of this, and related edible *Annona* species, yield upon extraction a mixture of highly insecticidal natural products known as acetogenins. Again, a waste product from one industry could serve as an inexpensive and readily available source of starting biomass for another industry.

Sawdust, bark and other wood waste generated from tropical timber harvesting and lumber production could, in certain cases, serve as an abundant natural resource from which natural insecticides could be extracted. Several members of the mahogany family (Meliaceae), to which neem and chinaberry (*Melia azedarach*) belong, are economically important timber species, and the wood and bark of some of these contain appreciable concentrations of limonoids that have antifeedant and/or growth inhibitory properties against pest insects (see refs. 3, 11). Important timber species in the family include mahogany (*Swietenia* spp.), African mahoganies (*Khaya* and *Entandophragma* spp.), and Spanish and Asian cedars (*Cedrela* and *Toona* spp.) (10).

Finally, tissue culture is a potential process for the production of bioactive natural products without the reliance on plants growing in the field and technology to harvest the desired part of the plant. Callus cultures of *A. indica* have been shown to produce azadirachtin and other bioactive limonoids. Whereas the yield of azadirachtin in initial cultures was low, yields in cell suspension cultures have been improved over 100–fold through optimization studies (14).

STANDARDIZATION AND QUALITY CONTROL

Natural defenses of plants against herbivory consist almost always of mixtures of closely related compounds, rather than a single toxicant alone. This phenomenon is well exemplified among botanical insecticides. Technical grade pyrethrum (the oleoresin remaining from extraction of the flower heads) contains four insecticidal esters, technical rotenone contains six or more insecticidal isoflavonoids, and neem contains up to a dozen azadirachtin analogs. In neem, two compounds (azadirachtins A and B) account for the majority of the bioactivity.

What are the advantages of using such complex mixtures? Firstly, there is evidence that these natural mixtures act synergistically. In other words, the overall efficacy is superior to that which could be obtained with the equivalent amount of the most active constituent alone, if isolated to purity or synthesized. This phenomenon was demonstrated over a decade ago (4). In my laboratory we observed that the growth inhibitory effect of refined bark extracts from *Melia toosendan*, containing 60–75% toosendanin, was significantly greater than that of pure toosendanin, indicating that lesser constituents were making a contribution to overall bioactivity greater than expected based on their mass (5).

Complex mixtures of active constituents, as found in botanical insecticides, may also be advantageous in terms of pest resistance and behavioral desensitization. In a laboratory selection experiment we demonstrated recently that the green peach aphid, *Myzus persicae*, was capable of evolving nine–fold resistance to azadirachtin over 35 generations when the selecting agent was pure azadirachtin applied to plants at the LC_{50} level. However, a parallel aphid line selected with a neem seed extract, containing the same absolute amount of azadirachtin but as part of a complex mixture, did not evolve resistance to azadirachtin over the same period (6). These results suggest that other compounds in the neem extract may diffuse the selection process, thus mitigating the development of resistance.

Whereas the possibility that insects will not develop resistance as quickly to a botanical insecticide as to a synthetic insecticide, the main reason for using a botanical insecticide is a practical one. Specifically, it is too difficult or costly either to isolate the principal active ingredient or synthesize it. The only exception to this statement concerns pyrethrum, where the active principle was not only synthesized, but provided the lead to an entire class of synthetic insecticides, the photostable pyrethroids. Nonetheless, natural pyrethrum remains in use and is cost effective in many market segments.

Whereas there are advantages to complex mixtures as pest control products, mixtures have certain disadvantages as well. The main problems they pose are related to the issues of standardization and quality control. Botanical insecticides, like conventional ones, should contain a specified concentration of active ingredient as an assurance that the product will perform as intended. How does one standardize a product when it contains a half-dozen or more active constituents of differing proportions and bioactivity?

In the case of pyrethrum, the resin is standardized based on the concentrations of the two pyrethrin esters (*e.g.* 20% pyrethrins). In the case of neem, two analogs of azadirachtin predominate, namely azadirachtin proper (sometimes referred to as 'aza A'), and 3-tigloylazadirachtol (commonly called 'aza B') (8). Since many analytical HPLC methods fail to resolve these major azadirachtin analogs, reported concentrations of azadirachtin may actually represent the sum of these two active principles.

The important point I raise is that there need be some quantifiable active ingredient(s) for commercial and regulatory purposes. If several active compounds require quantitation, analysis will be more difficult. Furthermore, natural products are notoriously variable, and therefore consistency of the final product will be much harder to achieve. Also, it may be necessary to determine both the shelf stability of the active ingredient and its fate in the environment or in animals. Such studies can be complicated enough when only a single compound is being tracked, but the effort required to track several putative active principles in a single product cannot be underestimated.

REGULATORY REQUIREMENTS

Even if the issues of natural resource abundance and chemical standardization can be dealt with satisfactorily, a new botanical insecticide must undergo the scrutiny of regulatory authorities prior to the product's entry into the marketplace, at least in industrialized countries. The following comments reflect the current situation in countries such as the USA, Germany and Japan, *i.e.*, those that have the highest standards for occupational and environmental health and safety. The costs for studies in support of registration of a new active ingredient in the USA can easily exceed US $250,000 and can potentially exceed US $2 million. As I often point out to small and start-up companies in the private sector, not a single dollar in revenue can be generated through sales without regulatory approval.

On the surface, the registration of a new botanical insecticide is a formidable task. It is fair to say that the regulatory assessment of pesticides 'grew up' with the agrochemical industry, and the regulatory protocols in place today are designed specifically around synthetic chemicals in a reasonable state of purity. Trying to move a complex mixture, as found in a botanical insecticide, through this system is somewhat a case of fitting a round peg into a square hole.

When Canadian regulatory authorities were first contacted regarding a neem-based insecticide, they asked for identification of every component of the refined extract (= technical grade active concentrate) making up at least 0.1% by weight of the extract. Because neem is a complex mixture, such characterization could take a year or more and cost tens of thousands of dollars. Earlier this year, the Pest Management Regulatory Agency approved an experimental use permit allowing the aerial application of neem for control of forest-defoliating sawflies based on our HPLC analysis of the neem concentrate in which the major ten limonoids, accounting for 90% of the UV-visible material, were identified and quantified.

Apparently there is room for compromise between what information is desirable for the regulatory agency and what can be practically provided by the applicant. The EPA in the USA has recently shown 'benevolence' toward 'reduced-risk' pesticides. In the case of a complex mixture like neem, they recognize many constituents as being benign. Philosophically, both the regulatory agency and the registrant want the product to be identical every time it is manufactured, but there is acknowledgment by both of the natural variation found in biological material. Thus, the importance of standardization must be emphasized.

As a generality, botanical insecticides are environmentally non-persistent. However, botanicals can have important impacts on non-target organisms, and even pose a risk to human health. It is clearly erroneous to assume that all botanical preparations are safe for humans; one need only refer to strychnine and nicotine for examples of plant natural products that have considerable toxicity to laboratory animals and that pose an appreciable risk to human health. Again, though, there may be room for regulatory compromise.

Because the large multinational corporations have no interest in the development of botanicals *per se*, efforts aimed at commercialization are being made by small and medium-sized companies, for whom the costs of long-term studies can pose a serious barrier. As there is political will aimed at increasing opportunities for 'reduced-risk' pesticides as alternatives to conventional synthetic ones, perhaps this will should be translated into a modified requirement for botanical products. One such mechanism to achieve this goal would be the allowance of provisional registration, based on submission of data from the battery of acute tests and wildlife studies. Assuming the outcome of the acute tests is favorable, a provisional registration would allow the manufacturer to begin marketing the botanical insecticide (perhaps in a geographically restricted area, or restricted to certain low-risk uses) to generate revenue, with the understanding that the registrant would have to provide data for the long-term tests and other data requirements within a 2–5-year period. Such a system exists in India, where applicants are allowed to market new products for up to 5 years before the final regulatory decision is made. While none of the western countries has yet adopted this policy, there is a move toward pre-registration consultation meetings between applicants and regulatory officials, with the possibility that certain data requirements could be waived for certain products. At this point, regulatory agencies are proceeding cautiously (as their mandate demands), but new products are being considered on a case-by-case basis.

CONCLUSIONS

In this review I have tried to outline some unique, but not insurmountable, challenges to the development and commercialization of new botanical insecticides. It is unrealistic to expect botanicals (and microbial insecticides) completely to displace conventional synthetic insecticides in the foreseeable future, but botanicals and other natural insecticides should find increasing favor in applications where a premium is placed on environmental safety and there is a greater tolerance for the presence of insects and/or damage.

Neem provides a modern paradigm for the development of botanical insecticides, and many lessons learned from neem over the past decade can be applied to the development of future botanicals. While there may not be any plant-derived products that possess the wide array of assets enjoyed by neem, there are unquestionably other natural products for which the supply can be assured, commercial standards established, and the regulatory requirements met, all on an economically viable basis. It remains for creative members of the private sector, working with the technical support of the scientific community, to guide such products down the critical path that leads to the plant protection marketplace.

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