Annu. Rev. Entomol. 2006. 51:45–66
doi: 10.1146/annurev.ento.51.110104.151146

BOTANICAL INSECTICIDES, DETERRENTS, AND REPELLENTS IN MODERN AGRICULTURE AND AN INCREASINGLY REGULATED WORLD

Murray B. Isman
Faculty of Land and Food Systems, University of British Columbia,
Vancouver, British Columbia, V6T 1Z4, Canada; email: murray.isman@ubc.ca

Key Words pyrethrum, neem, essential oils, antifeedants, commercialization

■ **Abstract** Botanical insecticides have long been touted as attractive alternatives to synthetic chemical insecticides for pest management because botanicals reputedly pose little threat to the environment or to human health. The body of scientific literature documenting bioactivity of plant derivatives to arthropod pests continues to expand, yet only a handful of botanicals are currently used in agriculture in the industrialized world, and there are few prospects for commercial development of new botanical products. Pyrethrum and neem are well established commercially, pesticides based on plant essential oils have recently entered the marketplace, and the use of rotenone appears to be waning. A number of plant substances have been considered for use as insect antifeedants or repellents, but apart from some natural mosquito repellents, little commercial success has ensued for plant substances that modify arthropod behavior. Several factors appear to limit the success of botanicals, most notably regulatory barriers and the availability of competing products (newer synthetics, fermentation products, microbials) that are cost-effective and relatively safe compared with their predecessors. In the context of agricultural pest management, botanical insecticides are best suited for use in organic food production in industrialized countries but can play a much greater role in the production and postharvest protection of food in developing countries.

INTRODUCTION

The practice of using plant derivatives, or botanical insecticides as we now know them, in agriculture dates back at least two millennia in ancient China, Egypt, Greece, and India (86, 89). Even in Europe and North America, the documented use of botanicals extends back more than 150 years, dramatically predating discoveries of the major classes of synthetic chemical insecticides (e.g., organochlorines, organophosphates, carbamates, and pyrethroids) in the mid-1930s to 1950s. What is clear from recent history is that synthetic insecticides effectively relegated botanicals from an important role in agriculture to an essentially trivial position in the marketplace among crop protectants. However, history also shows that overzealous use of synthetic insecticides led to numerous problems unforeseen at the time of their introduction: acute and chronic poisoning of applicators, farmworkers, and even consumers; destruction of fish, birds, and other wildlife; disruption of natural biological control and pollination; extensive groundwater contamination, potentially threatening human and environmental health; and the evolution of resistance to pesticides in pest populations (35, 63, 70, 72).

Governments responded to these problems with regulatory action, banning or severely restricting the most damaging products and creating policies to replace chemicals of concern with those demonstrated to pose fewer or lesser risks to human health and the environment. In the United States, these policies are reflected by the definition of "reduced risk" pesticides by the Environmental Protection Agency in the early 1990s with their favored regulatory status, and by the Food Quality Protection Act (1996), which, in reappraising safe levels of pesticide residues in foods, is having the net effect of removing most synthetic insecticides developed before 1980 from use in agriculture. These changes in the regulatory "environment" appeared to heighten the impetus for the discovery and development of alternative pest management products—those with reduced health and environmental impacts—including insecticides derived from plants. Indeed, the scientific literature of the past 25 years describes hundreds of isolated plant secondary metabolites that show feeding deterrent or toxic effects to insects in laboratory bioassays, and botanical insecticides have been the subject of several recent volumes (28, 40, 57, 76, 79).

Yet in spite of the scale of this research enterprise, only a handful of botanical insecticides are in commercial use on vegetable and fruit crops today, with significant commercial development of only two new sources of botanicals in the past 20 years. In this chapter I review current botanicals and their trends in use, discuss the few botanical materials with potential for future commercialization, suggest why so few botanicals reach the marketplace, and finally suggest in what contexts botanicals could prove effective in the years to come.

CURRENT BOTANICALS IN USE

At present there are four major types of botanical products used for insect control (pyrethrum, rotenone, neem, and essential oils), along with three others in limited use (ryania, nicotine, and sabadilla). Additional plant extracts and oils (e.g., garlic oil, *Capsicum* oleoresin) see limited (low volume) regional use in various countries, but these are not considered here. In discussing the extent to which each of the more important botanical insecticides is used, I often refer to data published annually by the State of California's Department of Pesticide Regulation (18). Although not necessarily representative of uses in other jurisdictions, total pesticide use (in terms of active ingredient applied) in California totaled more than 175 million pounds, or 80,000 tonnes, in 2003. This amount represents approximately 6% of global pesticide use, of which 91% was used for agriculture. Pesticide use data in California are reported by active ingredient and by crop or other use and as such are perhaps the world's most accurate and detailed records of pesticide use available to the general public.

Pyrethrum

Pyrethrum refers to the oleoresin extracted from the dried flowers of the pyrethrum daisy, *Tanacetum cinerariaefolium* (Asteraceae). The flowers are ground to a powder and then extracted with hexane or a similar nonpolar solvent; removal of the solvent yields an orange-colored liquid that contains the active principles (21, 37). These are three esters of chrysanthemic acid and three esters of pyrethric acid. Among the six esters, those incorporating the alcohol pyrethrolone, namely pyrethrins I (Figure 1) and II, are the most abundant and account for most of the insecticidal activity. Technical grade pyrethrum, the resin used in formulating commercial insecticides, typically contains from 20% to 25% pyrethrins (21).

The insecticidal action of the pyrethrins is characterized by a rapid knockdown effect, particularly in flying insects, and hyperactivity and convulsions in most insects. These symptoms are a result of the neurotoxic action of the pyrethrins, which block voltage-gated sodium channels in nerve axons. As such, the mechanism of action of pyrethrins is qualitatively similar to that of DDT and many synthetic organochlorine insecticides. In purity, pyrethrins are moderately toxic to mammals (rat oral acute LD_{50} values range from 350 to 500 mg kg^{-1}), but technical grade pyrethrum is considerably less toxic ($\sim$1500 mg kg^{-1}) (21). Pyrethrins are especially labile in the presence of the UV component of sunlight, a fact that has greatly limited their use outdoors. A recent study indicated that the half-lives of pyrethrins on field-grown tomato and bell pepper fruits were 2 hours or less (3).

This problem created the impetus for the development of synthetic derivatives ("pyrethroids") that are more stable in sunlight. The modern pyrethroids, developed in the 1970s and 1980s, have been highly successful and represent one of the rare examples of synthetic pesticide chemistry based on a natural product model. However, note that the modern pyrethroids bear little structural resemblance to the natural pyrethrins, and their molecular mechanism of action differs as well. Pyrethrum use data from California (18) in 2003 clearly demonstrate the dominance of this material among botanicals: Pyrethrum accounted for 74% of all botanicals used that year, but only 27% of that amount was used in agriculture ($\sim$800 kg). Major uses of pyrethrum in California are for structural pest control, in public health, and for treatment of animal premises. Pyrethrum is the predominant botanical in use, perhaps accounting for 80% of the global botanical insecticide market (49).

For many years world production of pyrethrum was led by Kenya, with lesser quantities produced in Tanzania and Ecuador. In the past five years, Botanical Resources Australia, with plantings in Tasmania, has become the second largest producer in the world ($\sim$30% of world production at present). Pyrethrum produced in Tasmania is qualitatively similar to that produced in East Africa and elsewhere, but the market share achieved by the Australian producer may not increase owing to World Bank grants and government subsidies to producers in Kenya and China (B. Chung, personal communication).

Neem

Two types of botanical insecticides can be obtained from seeds of the Indian neem tree, *Azadirachta indica* (Meliaceae) (81). Neem oil, obtained by cold-pressing seeds, can be effective against soft-bodied insects and mites but is also useful in the management of phytopathogens. Apart from the physical effects of neem oil on pests and fungi, disulfides in the oil likely contribute to the bioactivity of this material. More highly valued than neem oil are medium-polarity extracts of the seed residue after removal of the oil, as these extracts contain the complex triterpene azadirachtin (Figure 2). Neem seeds actually contain more than a dozen azadirachtin analogs, but the major form is azadirachtin and the remaining minor analogs likely contribute little to overall efficacy of the extract. Seed extracts include considerable quantities of other triterpenoids, notably salannin, nimbin, and derivatives thereof. The role of these other natural substances has been controversial, but most evidence points to azadirachtin as the most important active principle (50). Neem seeds typically contain 0.2% to 0.6% azadirachtin by weight, so solvent partitions or other chemical processes are required to concentrate this active ingredient to the level of 10% to 50% seen in the technical grade material used to produce commercial products.

Azadirachtin has two profound effects on insects. At the physiological level, azadirachtin blocks the synthesis and release of molting hormones (ecdysteroids) from the prothoracic gland, leading to incomplete ecdysis in immature insects. In adult female insects, a similar mechanism of action leads to sterility. In addition, azadirachtin is a potent antifeedant to many insects. The discovery of neem by western science is attributed to Heinrich Schmutterer, who observed that swarming desert locusts in Sudan defoliated almost all local flora except for some introduced neem trees (69). Indeed, azadirachtin was first isolated based on its exceptional antifeedant activity in the desert locust, and this substance remains the most potent locust antifeedant discovered to date. Unlike pyrethrins, azadirachtin has defied total synthesis to this point. Promoted in the United States by Robert Larson (with assistance from the U.S. Department of Agriculture), neem rapidly became the modern paradigm for development of botanical insecticides.

Enthusiasm for neem was fostered by several international conferences in the 1980s and 1990s, and several volumes dedicated to neem and neem insecticides have been published (51, 69, 81). Unfortunately, neem's commercial success has fallen well short of the initial hype fueled by the explosive scientific literature surrounding it. In part this is due to the relatively high cost of the refined product (48) and the relatively slow action on pest insects. Nonetheless, several azadirachtin-based insecticides are sold in the United States and at least two such products in the European Union. In California, azadirachtin-based insecticides constituted about one third of the botanicals used in agriculture in 2003 (~600 kg). In practice, reliable efficacy is linked to the physiological action of azadirachtin as an insect growth regulator; the antifeedant effect, which is spectacular in the desert locust, is highly variable among pest species, and even those species initially deterred are often capable of rapid desensitization to azadirachtin (13).

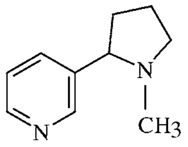
What is clear is that azadirachtin is considered nontoxic to mammals (rat oral acute LD_{50} is >5000 mg kg^{-1}), fish (88), and pollinators (71). The influence of azadirachtin on natural enemies is highly variable (62, 83). Like the pyrethrins, azadirachtin is rapidly degraded by sunlight. For example, on olives growing in Italy, azadirachtin has a half-life of approximately 20 h (16). On the other hand, azadirachtin has systemic action in certain crop plants, greatly enhancing its efficacy and field persistence (81).

Plant Essential Oils

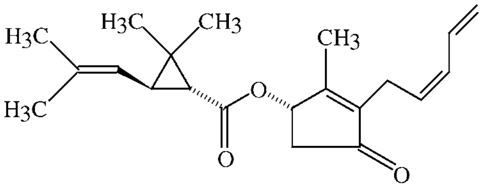
Steam distillation of aromatic plants yields essential oils, long used as fragrances and flavorings in the perfume and food industries, respectively, and more recently for aromatherapy and as herbal medicines (14, 26). Plant essential oils are produced commercially from several botanical sources, many of which are members of the mint family (Lamiaceae). The oils are generally composed of complex mixtures of monoterpenes, biogenetically related phenols, and sesquiterpenes. Examples include 1,8-cineole, the major constituent of oils from rosemary (*Rosmarinus officinale*) and eucalyptus (*Eucalyptus globus*); eugenol from clove oil (*Syzygium aromaticum*); thymol from garden thyme (*Thymus vulgaris*); and menthol from various species of mint (*Mentha* species) (45) (Figure 2). A number of the source plants have been traditionally used for protection of stored commodities, especially in the Mediterranean region and in southern Asia, but interest in the oils was renewed with emerging demonstration of their fumigant and contact insecticidal activities to a wide range of pests in the 1990s (46). The rapid action against some pests is indicative of a neurotoxic mode of action, and there is evidence for interference with the neuromodulator octopamine (29, 56) by some oils and with GABA-gated chloride channels by others (77).

Some of the purified terpenoid constituents of essential oils are moderately toxic to mammals, but, with few exceptions, the oils themselves or products based on oils are mostly nontoxic to mammals, birds, and fish (46, 84). However, as broad-spectrum insecticides, both pollinators and natural enemies are vulnerable to poisoning by products based on essential oils. Owing to their volatility, essential oils have limited persistence under field conditions; therefore, although natural enemies are susceptible via direct contact, predators and parasitoids reinvading a treated crop one or more days after treatment are unlikely to be poisoned by residue contact as often occurs with conventional insecticides.

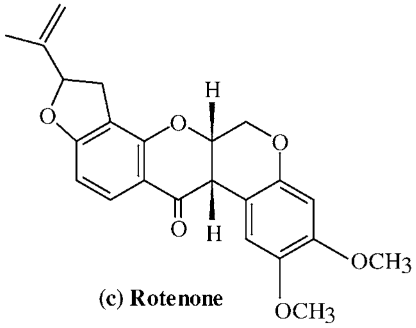
In the United States, commercial development of insecticides based on plant essential oils has been greatly facilitated by exemption from registration for certain oils commonly used in processed foods and beverages (78). This opportunity



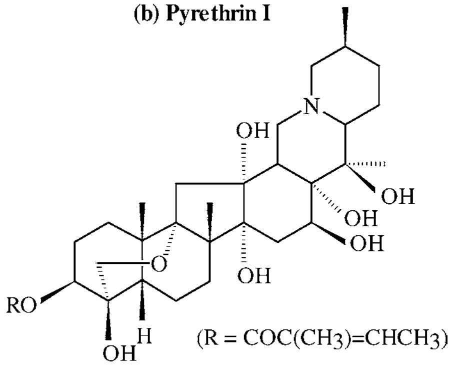
(a) Nicotine



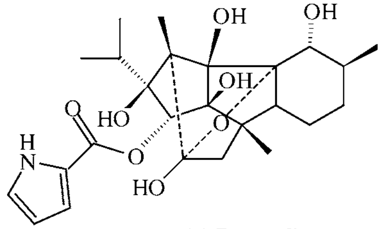
(b) Pyrethrin I



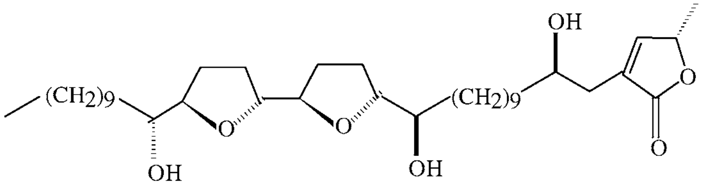
(c) Rotenone



(d) Cevadine

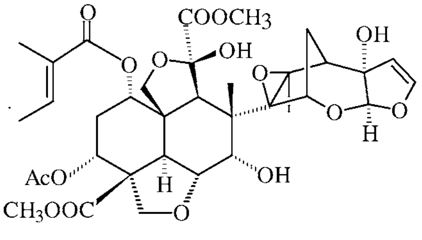


(e) Ryanodine

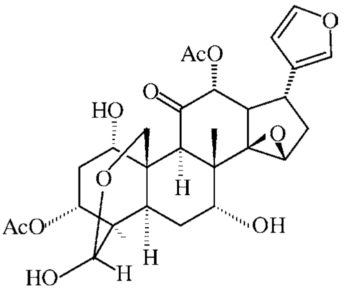


(f) Asimicin

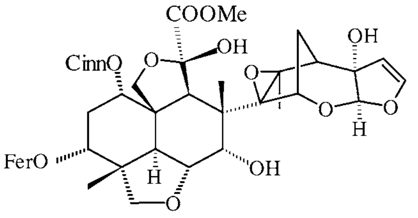
Figure 1 Active constituents of some botanical insecticides from various plant sources discussed in this review. (*a*) Nicotine, (*b*) pyrethrin I, (*c*) rotenone, (*d*) cevadine, (*e*) ryanodine, and (*f*) asimicin.



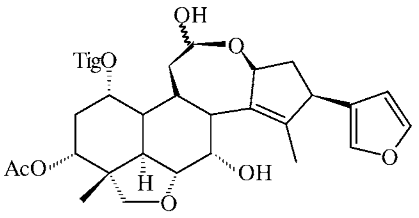
(a) Azadirachtin



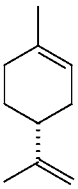
(b) Toosendanin



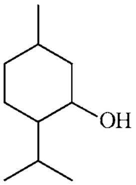
(c) 1-Cinnamoyl-3-feruoyl-11-hydroxymeliacarpin



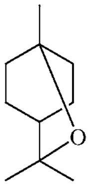
(d) Volkensin



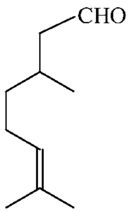
(e) *d*-Limonene



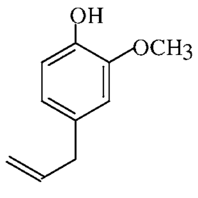
(f) Menthol



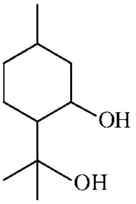
(g) 1,8-Cineole



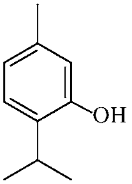
(h) Citronellal



(i) Eugenol



(j) *p*-Menthane-3,8-diol



(k) Thymol

Figure 2 Active constituents of some botanical insecticides from neem (*a*), *Melia* species (*b–d*), and selected plant essential oils (*e–k*). (*a*) Azadirachtin, (*b*) toosendanin, (*c*) 1-cinnamoyl-3-feruoyl-11-hydroxymeliacarpin, (*d*) volkensin, (*e*) *d*-limonene, (*f*) menthol, (*g*) 1,8-cineole, (*h*) citronellal, (*i*) eugenol, (*j*) *p*-menthane-3,8-diol, and (*k*) thymol.

has spurred the development of essential oil-based insecticides, fungicides, and herbicides for agricultural and industrial applications and for the consumer market, using rosemary oil, clove oil, and thyme oil as active ingredients. Interest in these products has been considerable, particularly for control of greenhouse pests and diseases and for control of domestic and veterinary pests, with several private companies (e.g., EcoSMART Technologies, Inc., United States) moving toward or into the marketplace. Another factor favoring development of botanical insecticides based on plant essential oils is the relatively low cost of the active ingredients, a result of their extensive worldwide use as fragrances and flavorings. In contrast, pyrethrum and neem are used primarily for insecticide production (R. Georgis, personal communication).

Rotenone and Other Extant Botanicals

As an insecticide, rotenone has been in use for more than 150 years, but its use as a fish poison dates back even further (82). Rotenone is one of several isoflavonoids produced in the roots or rhizomes of the tropical legumes *Derris*, *Lonchocarpus*, and *Tephrosia*. Most rotenone used at present comes from *Lonchocarpus* grown in Venezuela and Peru and is often called cubé root. Extraction of the root with organic solvents yields resins containing as much as 45% total rotenoids; studies indicate that the major constituents are rotenone (44%) (Figure 1) and deguelin (22%) (15, 30). Rotenone is commonly sold as a dust containing 1% to 5% active ingredients for home and garden use, but liquid formulations used in organic agriculture can contain as much as 8% rotenone and 15% total rotenoids.

Rotenone is a mitochondrial poison, which blocks the electron transport chain and prevents energy production (41). As an insecticide it is considered a stomach poison because it must be ingested to be effective. Pure rotenone is comparable to DDT and other synthetic insecticides in terms of its acute toxicity to mammals (rat oral LD_{50} is 132 mg kg^{-1}), although it is much less toxic at the levels seen in formulated products. Safety of rotenone has recently been called into question because of (*a*) controversial reports that acute exposure in rats produces brain lesions consistent with those observed in humans and animals with Parkinson's disease (10), and (*b*) the persistence of rotenone on food crops after treatment. A study of rotenone residues on olives conducted in Italy determined that the half-life of rotenone is 4 days, and at harvest residue levels were above the tolerance limit (17). Moreover, residues were concentrated in oil obtained from the olives. As an agricultural insecticide, use of rotenone is limited to organic food production. In California, about 200 kg are used annually, mostly on lettuce and tomato crops.

Sabadilla is a botanical insecticide obtained from the seeds of the South American lily *Schoenocaulon officinale*. In purity, the active principles, cevadine-type alkaloids (Figure 1), are extremely toxic to mammals (rat oral LD_{50} is ~13 mg kg^{-1}), but commercial preparations typically contain less than 1% active ingredient, providing a margin of safety. The mode of action of these alkaloids is remarkably similar to that of the pyrethrins, despite their lack of structural similarity. Sabadilla is used primarily by organic growers; in California about 100 kg is used annually, primarily on citrus crops and avocado. Another botanical in declining use is ryania, obtained by grinding the wood of the Caribbean shrub *Ryania speciosa* (Flacourtiaceae). The powdered wood contains $<1\%$ ryanodine (Figure 1), an alkaloid that interferes with calcium release in muscle tissue (70). It is used to a limited extent by organic apple growers for control of the codling moth, *Cydia pomonella*. More information on sabadilla and ryania can be found in a recent review (90).

Like pyrethrum and rotenone, nicotine, an alkaloid obtained from the foliage of tobacco plants (*Nicotiana tabacum*) and related species, has a long history as an insecticide. Nicotine (Figure 1) and two closely related alkaloids, nornicotine and anabasine, are synaptic poisons that mimic the neurotransmitter acetylcholine. As such, they cause symptoms of poisoning similar to those seen with organophosphate and carbamate insecticides (39). Owing to the extreme toxicity of pure nicotine to mammals (rat oral LD_{50} is 50 mg kg^{-1}) and its rapid dermal absorption in humans, nicotine has seen declining use, primarily as a fumigant in greenhouses against soft-bodied pests. However, there remains some interest in preparing stable nicotine fatty acid soaps, presumably with reduced bioavailability and toxicity to humans (20).

POTENTIAL NEW BOTANICALS

Annonaceous Acetogenins

Botanical insecticides have been traditionally prepared from the seeds of tropical *Annona* species, members of the custard apple family (Annonaceae). These include the sweetsop (*A. squamosa*) and soursop (*A. muricata*), important sources of fruit juices in Southeast Asia. Detailed investigations in the 1980s led to the isolation of a number of long-chain fatty acid derivatives, termed acetogenins, responsible for the insecticidal bioactivity. The major acetogenin obtained from seeds of *A. squamosa* is annonin I, or squamocin, and a similar compound, asimicin (Figure 1), was isolated from the bark of the American pawpaw tree, *Asimina triloba* (53, 65). McLaughlin and colleagues (66) hold a U.S. patent on insecticides based on acetogenins from *A. triloba*; Bayer AG (Germany) holds a similar patent based on *Annona* acetogenins (67). These compounds are slow acting stomach poisons, particularly effective against chewing insects such as lepidopterans and the Colorado potato beetle (*Leptinotarsa decemlineata*).

Further investigations revealed that the acetogenins have a mode of action identical to that of rotenone, i.e., they block energy production in mitochondria in both insects and mammals (61). In purity certain acetogenins are toxic to mammals (LD_{50} is <20 mg kg^{-1}), an impediment to regulatory approval, even though standardized extracts from *Annona* seeds and *Asimina* bark are much less toxic. McLaughlin and associates (53) have isolated hundreds of acetogenins from the Annonaceae, and for many their potential as anticancer agents exceeds their value as insecticides. In spite of the patents based on the insecticidal activities of these materials, no commercial development has proceeded with the exception of a head lice shampoo that contains a standardized pawpaw extract among its active ingredients (Nature's Sunshine Products, Inc., United States). *Annona* seed extracts may prove more useful in tropical countries where the fruits are commonly consumed or used to produce fruit juice, in which case the seeds are a waste product. For example, Leatemia & Isman (59, 60) recently demonstrated that crude ethanolic extracts or even aqueous extracts of seeds from *A. squamosa* collected at several sites in eastern Indonesia are effective against the diamondback moth (*Plutella xylostella*).

Sucrose Esters

In the early 1990s scientists at the U.S. Department of Agriculture discovered that sugar esters naturally occurring in the foliage of wild tobacco (*Nicotiana gossei*) were insecticidal to certain soft-bodied insects and mites. Although patented (75), extraction of these substances on a commercial scale from plant biomass proved impractical, leading to the development of sucrose esters manufactured from sugar and fatty acids obtained from vegetable oils. AVA Chemical Ventures (United States) has patented and registered an insecticide/miticide based on C_8 and C_{10} fatty acid mono-, di-, and triesters of sucrose octanoate and sucrose dioctanoate (31). The product, first registered in 2002, contains 40% active ingredient. Functionally, this product appears to differ little from the insecticidal soaps based on fatty acid salts developed in the 1980s, particularly potassium oleate. Both products are contact insecticides that kill small insects and mites through suffocation (by blocking the spiracles) or disruption of cuticular waxes and membranes in the integument, leading to desiccation. Although useful in home and garden products and in greenhouse production, the utility of these materials for agriculture remains to be seen.

Melia Extracts

The remarkable bioactivity of azadirachtin from the Indian neem tree (*Azadirachta indica*) led to the search for natural insecticides in the most closely related genus, *Melia*. Seeds from the chinaberry tree, *M. azedarach*, contain a number of triterpenoids, the meliacarpins (Figure 2), that are similar but not identical to the azadirachtins, and these too have insect growth regulating bioactivities (58). But in spite of the abundance of chinaberry trees in Asia and other tropical and subtropical areas to which they were introduced, development of commercial insecticides has not paralleled that of the neem insecticides. The main reason is the presence, in chinaberry seeds, of additional triterpenoids, the meliatoxins, that have demonstrated toxicity to mammals (4). However the chemistry of chinaberry varies considerably across its natural and introduced range, and seeds of *M. azedarach* growing in Argentina lack meliatoxins but produce triterpenoids (most notably meliartenin) that are strong feeding deterrents to pest insects and could prove useful for pest management (19). Similar results have been obtained from South Africa using aqueous extracts of chinaberry leaves, presumably lacking meliatoxins but efficacious against the diamondback moth (22).

In the early 1990s a botanical insecticide produced in China was based on an extract of bark of *Melia toosendan*, a tree considered by most taxonomists to be synonymous with *M. azedarach*. The extract contains a number of triterpenoids based on toosendanin (Figure 2), a substance reported to be a stomach poison for chewing insects (24). Later studies suggest that this substance acts primarily as a feeding deterrent but can also serve as a synergist for conventional insecticides (23, 32). Although relatively nontoxic to mammals, it is unclear whether this material remains in production or whether it is sufficiently efficacious as a stand-alone crop protectant.

When *M. toosendan* came under scientific scrutiny, investigation of the east African *M. volkensii* demonstrated bioactivity in insects from seed extracts of this species. The active principles in *M. volkensii* include the triterpenoid salannin, also a major constituent of neem seed extracts, and some novel triterpenoids such as volkensin (Figure 2). Collectively these function as feeding deterrents and stomach poisons with moderate efficacy against chewing insects and as a mosquito larvicide. Although a standardized seed extract has been made in quantities sufficient for research (80), commercial production appears unlikely owing to a lack of infrastructure for harvesting seeds in addition to regulatory impediments.

INSECT ANTIFEEDANTS AND REPELLENTS

Antifeedants

The possibility of using nontoxic deterrents and repellents as crop protectants is intuitively attractive. The concept of using insect antifeedants (=feeding deterrents) gained strength in the 1970s and 1980s with the demonstration of the potent feeding deterrent effect of azadirachtin and neem seed extracts to a large number of pest species. Indeed, considerable literature, scientific and otherwise, touts neem as a successful demonstration of the antifeedant concept. In reality, it is the physiological actions of azadirachtin that appear most reliably linked to field efficacy of neem insecticides (42); although purely behavioral effects cannot be ruled out, there is hardly any irrefutable evidence or documentation of field efficacy based on the antifeedant effects of neem alone.

As an academic exercise, the discovery and demonstration of plant natural products as insect antifeedants has been unquestionably successful. In addition to the neem triterpenoids, extensive work has been performed on clerodane diterpenes from the Lamiaceae (55) and sesquiterpene lactones from the Asteraceae (38). On the other hand, not a single crop protection product based unequivocally on feeding or oviposition deterrence has been commercialized. Two main problems face the use of antifeedants in agriculture (47). The first is interspecific variation in response—even closely related species can differ dramatically in behavioral responses to a substance—limiting the range of pests affected by a particular antifeedant (43). Some substances that deter feeding by one pest can even serve as attractants or stimulants for other pests. The second is the behavioral plasticity in insects—pests can rapidly habituate to feeding deterrents, rendering them ineffective in a matter of hours. This has been recently demonstrated not only for pure substances like azadirachtin (13), but also for complex mixtures (plant extracts) (1). Whereas a highly mobile (flying) insect may leave a plant upon first encountering an antifeedant, a less mobile one (larva) may remain on the plant long enough for the deterrent response to wane. Such behavioral changes are important in light of the observation that some plant substances are initially feeding deterrents but lack toxicity if ingested. Azadirachtin is clearly an exception to this rule, as ingestion leads to deleterious physiological consequences, but many other compounds or extracts with demonstrated antifeedant effects lack toxicity when administered topically or via injection (8, 9).

Repellents

For many chemists, an effective alternative to DEET (N,N-diethyl-*m*-toluamide) for personal protection against mosquitoes and biting flies is the holy grail. In spite of five decades of research, no chemical has been found that provides the degree of protection against biting mosquitoes or persistence on human skin afforded by DEET (74). Concerns with the safety of DEET, especially to children, have resulted in the introduction of several plant oils as natural alternatives. Some personal repellents in the U.S. marketplace contain oils of citronella, eucalyptus, or cedarwood as active ingredients; 2-phenethylpropionate, a constituent of peanut oil, and *p*-menthane-3,8-diol (obtained from a particular species of mint) (Figure 2) are also used in consumer products. All of these materials can provide some protection, but the duration of their effect can be limited (often <1 h) (36). In tropical areas where mosquito-borne disease is a threat (e.g., yellow fever, dengue, malaria), DEET probably remains the only reliable repellent. Oil of citronella or the constituent citronellal (Figure 2) is also used in mosquito coils to repel mosquitoes from outdoor areas. Several veterinary products for flea and tick control on domestic pets contain *d*-limonene (from citrus peels; Figure 2) as the active ingredient. Other uses for repellents under investigation include perimeter treatments of buildings to exclude termites and the use of essential oils to repel cockroaches from kitchens and flies from dairy barns (64). Another important use of plant essential oil constituents is in fumigation of beehives to manage economically important honey bee parasites, the Varroa mite (*Varroa jacobsoni*) and the tracheal mite (*Acarapis woodi*). In North America, menthol (from peppermint; Figure 2) is widely used for this purpose (27), and in Europe thymol (from garden thyme; Figure 2) is most often used (34).

CURRENT TRENDS IN THE USE OF BOTANICALS

North America

At present, the United States allows the broadest range of botanical insecticides among industrialized countries, with registrations for pyrethrum, neem, rotenone, several essential oils, sabadilla, ryania, and nicotine (Table 1). Several azadirachtin-based (neem) insecticides are sold in the United States, and a number of plant essential oils are exempt from registration altogether. Canada has been more conservative with respect to pesticide registrations, allowing pyrethrum, rotenone, and nicotine, but only a handful of essential oils (73). Neem has yet to achieve full registration in Canada, to the disappointment of many organic growers. Mexico allows the use of most products sold in the United States, although there is no specific exemption for plant oils.

Europe

Although considered by many in the agrochemical industry to be especially restrictive with respect to pesticide registrations, the European Union permits the use of pyrethrum, neem, rotenone, and nicotine, along with "components of etheric oils

TABLE 1 Botanical insecticides approved for use in specific countries

Country	Pyrethrum	Rotenone	Nicotine	Neem[a]	Others
Australia	X	X	—	—	Citrus oils
New Zealand	X	X	—	X	
India	X	X	X	X	Ryania
Philippines	X	—	—	—	
Hungary	X	—	—	—	Quassia
Denmark	X	X	—	—	Lemongrass, clove, eucalyptus oils
Germany	X	—	—	X	
Netherlands	X	—	—	—	
United Kingdom	X	X	X	—	
South Africa	X	—	—	—	
Brazil	X	X	—	X	Garlic
United States	X	X	X	X	Specified essential oils, ryania, sabadilla
Canada	X	X	X	—	Specified essential oils
Mexico	X	X	—	X	Garlic, capsicum

[a] Includes insecticides listing azadirachtin as the active ingredient.

Source: Reference 73 and personal communications (D. Badulescu, B. Chung, J. Immaraju & J. Vendramin).

of plant origin" (73). Individual countries in western Europe show considerable variation in the botanicals they permit. For example, Hungary permits pyrethrum and nicotine, although the latter is severely restricted. Denmark permits only pyrethrum and rotenone, Germany pyrethrum and neem. The Netherlands permits pyrethrum alone. In spite of years of research on azadirachtin and neem in the United Kingdom, this botanical has never achieved registration there, leaving pyrethrum, rotenone, and nicotine as the only approved botanicals.

Pacific/Asia

India appears to embrace botanicals more than many other countries in the region, permitting all of the materials (save sabadilla) mentioned herein and allowing new products provisional registration while toxicological and environmental data in support of full registration are acquired. New Zealand has registrations for pyrethrum, rotenone, and neem, whereas Australia has yet to approve neem in spite of almost two decades of research and development in that country. Likewise, neem has yet to be approved for use in the Philippines, where pyrethrum is the only approved botanical insecticide.

Latin America

In Brazil, each state has autonomous regulatory authority. Botanicals registered in most states include pyrethrum, rotenone, neem, and garlic, although nicotine and extracts of native plants are used to a small extent (J. Vendramin, personal communication). Throughout Latin America plant oils and extracts are produced by cottage industries on a small scale and used outside of any regulatory system on a regional basis (D. Badulescu, personal communication).

Africa

Data on regulated insecticides are not readily available for most African countries. Among botanicals, only pyrethrum is approved for use in South Africa. As in Latin America, numerous crude plant extracts and oils are likely in local use in the poorer countries.

Trends and Changes in Registration

Given the ongoing negative perception of pesticides by the general public, government response to that perception, and increasing documentation of environmental contamination, it is hard to imagine pesticide regulators easing toxicological requirements for new pesticides, with the possible exception of certain plant oils and extracts widely used in human foods. Globalization of agricultural commodities will serve only to tighten restrictions on pesticide use in developing countries where fresh produce for export to wealthier countries is an important source of revenue. All produce imported into the European Union, United States, and Japan (for example) must comply with pesticide regulations in the respective importing country, meeting the same standards as their own domestic produce. As a result, pesticide regulations set in the wealthiest countries have global reach—they affect growers directly in developing countries who are forced to comply. In short, a lack of confidence in the safety of a specific botanical insecticide by the European Union could make that product unfavorable in a tropical country, even where it makes sense for poorer growers providing agricultural produce for their domestic markets, and perhaps where the botanical source material grows and could be inexpensively prepared for crop protection. If nothing else, this review should highlight the fact that few new botanical insecticides are likely to see commercialization on a meaningful scale in the near future, in spite of the continual discovery of plant natural products with bioactivity against insect pests.

DRAWBACKS AND BARRIERS TO COMMERCIALIZATION

In reviewing this subject previously (44), I identified three main barriers to commercialization for botanical insecticides: sustainability of the botanical resource, standardization of chemically complex extracts, and regulatory approval. For each of these there are also important cost considerations. Other drawbacks or limitations are the slow action of many botanicals—growers must gain confidence in insecticides that do not produce an immediate "knockdown" effect—and the lack of residual action for most botanicals.

Sustainability

To produce a botanical insecticide on a commercial scale, the source plant biomass must be obtainable on an agricultural scale and preferably not on a seasonal basis. Unless the plant in question is extremely abundant in nature, or already grown for another purpose (e.g., sweetsop, *Annona squamosa*, grown for its edible fruit; rosemary, *Rosmarinus officinale*, as a flavoring), it must be amenable to cultivation. Pyrethrum and neem meet this criterion; the latter has been extensively introduced into Africa, Australia, and Latin America, more so as a shade tree, windbreak, or source of firewood than for its yield of natural medicines or insecticides. Research aimed at producing azadirachtin from neem tissue culture provided proof of concept, but economic feasibility has yet to be attained (2).

In the not-too-distant future it may be possible to produce botanical insecticides by "phytopharming," i.e., through genetic engineering of an existing field crop to produce high-value natural products originally isolated from a different botanical source. But as progress in plant biotechnology continues at a rapid pace, it may prove just as easy to modify the plants we wish to protect from pests directly, such that they produce the natural product protectant constitutively, alleviating the need to obtain the desired botanical product through extraction, formulate it, and then apply it to the crop we wish to protect. These sorts of technological advancements seem far more likely now than they did even a decade ago; however, the cost of these technologies will dictate that the traditional means of obtaining botanical insecticides, and indeed their minor uses (on small acreage specialty crops) or uses in developing countries on lesser value crops will continue for many years to come. For example, neem seed oil had a long history of use in India for the production of soaps and low grade industrial oil. When extraction companies began purchasing neem seeds in bulk to produce insecticides, the price of seeds increased 10-fold. In contrast, certain plant essential oils have numerous uses as fragrances and flavorings, and the massive volumes required to satisfy these industries maintain low prices that make their use as insecticides attractive.

Standardization of Botanical Extracts

An often cited drawback to the adoption of botanical insecticides by growers is the variation in performance of a particular product, even when prepared by the same process. Natural variation in the chemistry of a plant-based commodity should come as no surprise to anyone who enjoys coffee, tea, wine, or chocolate. Recent investigation of seed extracts from sweetsop (*A. squamosa*) collected in Indonesia demonstrated both geographical and annual variation in their insecticidal potency (60). For a botanical insecticide to provide a reliable level of efficacy to the user, there must be some degree of chemical standardization, presumably based on the putative active ingredient(s). This has certainly been achieved with more refined products based on pyrethrum, neem, and rotenone, but crude preparations often contain low concentrations of active ingredients without adequate quantitation. To achieve standardization, the producer must have an analytical method and the equipment necessary for analysis and may need to mix or blend extracts from different sources, which requires storage facilities and is partially dependent on the inherent stability of the active principles in the source plant material or extracts thereof held in storage (5).

Regulatory Approval

Regulatory approval remains the most formidable barrier to the commercialization of new botanical insecticides. In many jurisdictions, no distinction is made between synthetic pesticides and biopesticides, including botanicals. Simply put, the market for botanicals in industrialized countries—based mostly on uses in greenhouse production and organic agriculture—is too small to generate sufficient profits to offset multimillion dollar regulatory costs. Unfortunately, this situation may prevent many “green” pesticides from reaching the marketplace in countries where the demand is greatest. I am not making the case that botanicals should be exempt from all regulatory scrutiny; as discussed above, nicotine is as toxic and hazardous as many synthetic insecticides, and strychnine, still used for rodent and insect control in some regions, is responsible for some human poisonings (54). Natural products can pose risks, and safety cannot be assumed (25, 87). But most of the botanicals discussed in this review are characterized by low mammalian toxicity, reduced effects on nontarget organisms, and minimal environmental persistence.

As noted, several plant essential oils and their constituents are exempt from registration in the United States, attributed to their long use history as food and beverage flavorings or as culinary spices. This exemption has facilitated the rapid development and commercialization of insecticides based on these materials as active ingredients (46). Although other jurisdictions have yet to follow the lead of the United States in this regard, there are proposals in some Asian countries to exempt some types of pesticides from registration for specific uses in public health, for example, in head lice preparations or for cockroach and fly suppression. It seems that regulatory agencies continue to focus their efforts on protecting the general public from miniscule traces of pesticides in the food supply rather than focusing on the safety of applicators and farmworkers, for whom, arguably, the more demonstrable hazards occur.

ROLE OF BOTANICALS IN THE FUTURE

What role can botanical insecticides play in crop protection and for other uses in the near future? In industrialized countries it is hard to imagine botanicals playing a greater role than at present, except in organic food production. Organic production is estimated to be growing by 8% to 15% per annum in Europe and in North America (70), and it is in those marketplaces that botanicals face the fewest competitors. Even there, however, microbial insecticides and spinosad have proven efficacious and cost-effective. Rather than considered as stand-alone products, botanicals might be better placed as products in crop protectant rotations, especially in light of the documented resistance of the diamondback moth to *Bacillus thuringiensis* and spinosad due to overuse (85, 91). In conventional agriculture, botanicals face tremendous competition from the newest generation of "reduced risk" synthetic insecticides such as the neonicotinoids. Between 1998 and 2003, use of reduced risk pesticides in California increased more than threefold (from 138 to 483 tons), whereas biopesticide use declined (from 652 to 472 tons) (18). Botanicals, constituting less than 1% of biopesticide use in California (18), are also in decline. Overall, it is hard not to conclude that the best role for botanicals in the wealthier countries is in public health (mosquito, cockroach abatement) and for consumer (home and garden) use.

The real benefits of botanical insecticides can be best realized in developing countries, where farmers may not be able to afford synthetic insecticides and the traditional use of plants and plant derivatives for protection of stored products is long established. Even where synthetic insecticides are affordable to growers (e.g., through government subsidies), limited literacy and a lack of protective equipment result in thousands of accidental poisonings annually (35).

Recent attention has been paid to traditional plants used in West Africa for postharvest protection against insects (6, 11, 12). Some of the more efficacious plants used have well-known active principles (e.g., rotenoids from *Tephrosia*, nicotine from *Nicotiana*, methyl salicylate from *Securidaca*, and eugenol from *Ocimum*); some of these are volatile and act as natural fumigants that kill adult pests and their progeny (52). At least one study indicates that these materials are relatively safe in the forms in which they are used (7). Some plant products could even be useful in industrialized countries for the protection of grain from storage pests (33).

Many of the plants discussed in this review are tropical in distribution and theoretically available to growers in developing countries. However, efficacy against pests is only one factor in the adoption of botanicals—logistics of production, preparation, or use of botanicals can mitigate against their use (68). Perhaps it is time to refocus the attention of the research community toward the development and application of known botanicals rather than screen more plants and isolate further novel bioactive substances that satisfy our curiosity but are unlikely to be of much utility.

ACKNOWLEDGMENTS

I thank NSERC (Canada) and EcoSMART Technologies, Inc., for supporting original research on botanical insecticides and antifeedants in my laboratory. Industrial colleagues in western Europe, Latin America, and Australia provided information on registered botanical insecticides in their regions.

The *Annual Review of Entomology* is online at http://ento.annualreviews.org

LITERATURE CITED

1. Akhtar Y, Rankin CH, Isman MB. 2003. Decreased response to feeding deterrents following prolonged exposure in the larvae of a generalist herbivore, *Trichoplusia ni* (Lepidoptera: Noctuidae). *J. Insect Behav.* 16:811–31
2. Allan EJ, Eeswara JP, Jarvis AP, Mordue Luntz AJ, Morgan ED, Stuchbury T. 2002. Induction of hairy root cultures of *Azadirachta indica* A. Juss. and their production of azadirachtin and other important insect bioactive metabolites. *Plant Cell Rep.* 21:374–79
3. Antonious GF. 2004. Residues and half-lives of pyrethrins on field-grown pepper and tomato. *J. Environ. Sci. Health* B39:491–503
4. Ascher KRS, Schmutterer H, Mazor M, Zebitz CPW, Naqvi SNH. 2002. The Persian lilac or chinaberry tree: *Melia azedarach* L. See Ref. 81, pp. 770–820
5. Atkinson BL, Blackman AJ, Faber H. 2004. The degradation of the natural pyrethrins in crop storage. *J. Agric. Food Chem.* 52:280–87
6. Belmain S, Stevenson P. 2001. Ethnobotanicals in Ghana: reviving and modernizing age-old farmer practice. *Pestic. Outlook* 12:233–38
7. Belmain SR, Neal GE, Ray DE, Golob P. 2001. Insecticidal and vertebrate toxicity associated with ethnobotanicals used as post-harvest protectants in Ghana. *Food Chem. Toxicol.* 39:287–91
8. Bernays EA. 1990. Plant secondary compounds deterrent but not toxic to the grass specialist acridid *Locusta migratoria*: implications for the evolution of graminivory. *Entomol. Exp. Appl.* 54:53–56

9. Bernays EA. 1991. Relationship between deterrence and toxicity of plant secondary compounds for the grasshopper *Schistocerca americana*. *J. Chem. Ecol.* 17:2519–26
10. Betarbet R, Sherer TB, MacKenzie G, Garcia-Osuna M, Panov AV, Greenamyre JT. 2000. Chronic systematic pesticide exposure reproduces features of Parkinson's disease. *Nature Neurosci.* 3:1301–6
11. Boeke SJ, Baumgart IR, van Loon JJA, van Huis A, Dicke M, Kossou DK. 2004. Toxicity and repellence of African plants traditionally used for the protection of stored cowpea against *Callosobruchus maculatus*. *J. Stored Prod. Res.* 40:423–38
12. Boeke SJ, Kossou DK, van Huis A, van Loon JJA, Dicke M. 2004. Field trials with plant products to protect stored cowpea against insect damage. *Int. J. Pest Manag.* 50:1–9
13. Bomford MK, Isman MB. 1996. Desensitization of fifth instar *Spodoptera litura* (Lepidoptera: Noctuidae) to azadirachtin and neem. *Entomol. Exp. Appl.* 81:307–13
14. Buckle J. 2003. *Clinical Aromatherapy: Essential Oils in Practice*. Edinburgh: Churchill Livingstone. 416 pp.
15. Cabizza M, Angioni A, Melis M, Cabras M, Tuberoso CV, Cabras P. 2004. Rotenone and rotenoids in cubé resins, formulations, and residues on olives. *J. Agric. Food Chem.* 52:288–93
16. Caboni P, Cabras M, Angioni A, Russo M, Cabras P. 2002. Persistence of azadirachtin residues on olives after field treatment. *J. Agric. Food Chem.* 50:3491–94
17. Cabras P, Caboni P, Cabras M, Angioni A, Russo M. 2002. Rotenone residues on olives and in olive oil. *J. Agric. Food Chem.* 50:2576–80
18. California Department of Pesticide Regulation. 2005. *Summary of pesticide use report data 2003, indexed by chemical.* http://www.cdpr.ca.gov/
19. Carpinella MC, Defago MT, Valladares G, Palacios SM. 2003. Antifeedant and insecticide properties of a limonoid from *Melia azedarach* (Meliaceae) with potential use for pest management. *J. Agric. Food Chem.* 51:369–74
20. Casanova H, Ortiz C, Peláez C, Vallejo A, Moreno ME, Acevedo M. 2002. Insecticide formulations based on nicotine oleate stabilized by sodium caseinate. *J. Agric. Food Chem.* 50:6389–94
21. Casida JE, Quistad GB. 1995. *Pyrethrum Flowers: Production, Chemistry, Toxicology and Uses*. Oxford, UK: Oxford Univ. Press. 356 pp.
22. Charleston DS. 2004. *Integrating biological control and botanical pesticides for management of* Plutella xylostella. PhD thesis. Wageningen Univ. 176 pp.
23. Chen W, Isman MB, Chiu SF. 1995. Antifeedant and growth inhibitory effects of the limonoid toosendanin and *Melia toosendan* extracts on the variegated cutworm, *Peridroma saucia* (Lep., Noctuidae). *J. Appl. Entomol.* 119:367–70
24. Chiu SF. 1988. Recent advances in research on botanical insecticides in China. In *Insecticides of Plant Origin*, ed. AT Arnason, BJR Philogène, P Morand, pp. 69–77. Washington, DC: Am. Chem. Soc.
25. Coats JR. 1994. Risks from natural versus synthetic insecticides. *Annu. Rev. Entomol.* 39:489–515
26. Coppen JJW. 1995. *Flavours and Fragrances of Plant Origin.* Rome: Food Agric. Org. 101 pp.
27. Delaplane KS. 1992. Controlling tracheal mites (Acari: Tarsonemidae) in colonies of honey bees (Hymenoptera: Apidae) with vegetable oil and menthol. *J. Econ. Entomol.* 85:2118–24
28. Dev S, Koul O. 1997. *Insecticides of Natural Origin*. Amsterdam: Harwood Acad. 365 pp.
29. Enan E. 2001. Insecticidal activity of essential oils: octopaminergic sites of action. *Comp. Biochem. Physiol.* 130C:325–37
30. Fang N, Casida J. 1998. Anticancer action of cubé insecticide: correlation for rotenoid constituents between inhibition of

NADH-ubiquinone oxidoreductase and induced ornithine decarboxylase activities. *Proc. Natl. Acad. Sci. USA* 95:3380–84

31. Farone WA, Palmer T, Puterka J. 2002. *U.S. Patent No. 6419941*
32. Feng R, Chen W, Isman MB. 1995. Synergism of malathion and inhibition of midgut esterase activities by an extract from *Melia toosendan* (Meliaceae). *Pestic. Biochem. Physiol.* 53:34–41
33. Fields PG, Xie YS, Hou X. 2001. Repellent effect of pea (*Pisum sativum*) fractions against stored-product pests. *J. Stored Prod. Res.* 37:359–70
34. Floris I, Satta A, Cabras P, Garau VL, Angioni A. 2004. Comparison between two thymol formulations in the control of *Varroa destructor*: effectiveness, persistence and residues. *J. Econ. Entomol.* 97:187–91
35. Forget G, Goodman T, de Villiers A, eds. 1993. *Impact of Pesticide Use on Health in Developing Countries.* Ottawa: Int. Dev. Res. Centre. 335 pp.
36. Fradin MS, Day JF. 2002. Comparative efficacy of insect repellents against mosquito bites. *N. Engl. J. Med.* 347:13–18
37. Glynne-Jones A. 2001. Pyrethrum. *Pestic. Outlook* 12:195–98
38. Gonzalez-Coloma A, Valencia F, Martin N, Hoffmann JJ, Hutter L, et al. 2002. Silphinene sesquiterpenes as model insect antifeedants. *J. Chem. Ecol.* 28:117–29
39. Hayes WJ Jr. 1982. *Pesticides Studied in Man.* Baltimore: Williams & Wilkins. 672 pp.
40. Hedin PA, Hollingworth RM, Masler EP, Miyamoto J, Thompson DG, eds. 1997. *Phytochemicals for Pest Control.* Washington, DC: Am. Chem. Soc. 372 pp.
41. Hollingworth R, Ahmmadsahib K, Gedelhak G, McLaughlin J. 1994. New inhibitors of complex I of the mitochondrial electron transport chain with activity as pesticides. *Biochem. Soc. Trans.* 22:230–33
42. Immaraju JA. 1998. The commercial use of azadirachtin and its integration into viable pest control programmes. *Pestic. Sci.* 54:285–89
43. Isman MB. 1993. Growth inhibitory and antifeedant effects of azadirachtin on six noctuids of regional economic importance. *Pestic. Sci.* 38:57–63
44. Isman MB. 1997. Neem and other botanical insecticides: barriers to commercialization. *Phytoparasitica* 25:339–44
45. Isman MB. 1999. Pesticides based on plant essential oils. *Pestic. Outlook* 10:68–72
46. Isman MB. 2000. Plant essential oils for pest and disease management. *Crop Prot.* 19:603–8
47. Isman MB. 2002. Insect antifeedants. *Pestic. Outlook* 13:152–57
48. Isman MB. 2004. Factors limiting commercial success of neem insecticides in North America and Western Europe. In *Neem: Today and in the New Millennium*, ed. O Koul, S Wahab, pp. 33–41. Dordrecht: Kluwer Acad.
49. Isman MB. 2005. Problems and opportunities for the commercialization of botanical insecticides. In *Biopesticides of Plant Origin*, ed. C Regnault-Roger, BJR Philogène, C Vincent, pp. 283–91. Paris: Lavoisier
50. Isman MB, Matsuura H, MacKinnon S, Durst T, Towers GHN, Arnason JT. 1996. Phytochemistry of the Meliaceae. So many terpenoids, so few insecticides. In *Phytochemical Diversity and Redundancy*, ed. JT Romeo, JA Saunders, P Barbosa, pp. 155–78. New York: Plenum
51. Jacobson M, ed. 1989. *Focus on Phytochemical Pesticides*. Vol. 1: *The Neem Tree.* Boca Raton, FL: CRC Press. 178 pp.
52. Jayasekara TK, Stevenson PC, Hall DR, Belmain SR. 2005. Effect of volatile constituents from *Securidaca longepedunculata* on insect pests of stored grain. *J. Chem. Ecol.* 31:303–13
53. Johnson HA, Oberlies NH, Alali FQ, McLaughlin JE. 2000. Thwarting resistance: annonaceous acetogenins as new pesticidal and antitumor agents. In *Biological Active Natural Products: Pharmaceuticals*, ed. SJ Cutler, JG Cutler, pp. 173–83. Boca Raton, FL: CRC Press

54. Katz J, Prescott K, Woolf AD. 1996. Strychnine poisoning from a Cambodian traditional remedy. *Am. J. Emerg. Med.* 14: 475–77
55. Klein Gebbinck EA, Jansen BJM, de Groot A. 2002. Insect antifeedant activity of clerodane dieterpenes and related model compounds. *Phytochemistry* 61:737–70
56. Kostyukovsky M, Rafaeli A, Gileadi C, Demchenko N, Shaaya E. 2002. Activation of octopaminergic receptors by essential oil constituents isolated from aromatic plants: possible mode of action against insect pests. *Pest Manag. Sci.* 58:1101–6
57. Koul O, Dhaliwal GS. 2001. *Phytochemical Biopesticides*. Amsterdam: Harwood Acad. 223 pp.
58. Kraus W. 2002. Azadirachtin and other triterpenoids. See Ref. 81, pp. 39–111
59. Leatemia JA, Isman MB. 2004. Efficacy of crude seed extracts of *Annona squamosa* against diamondback moth, *Plutella xylostella* L. in the greenhouse. *Int. J. Pest Manag.* 50:129–33
60. Leatemia JA, Isman MB. 2004. Insecticidal activity of crude seed extracts of *Annona* spp., *Lansium domesticum* and *Sandoricum koetjape* against lepidopteran larvae. *Phytoparasitica* 32:30–37
61. Londershausen M, Leight W, Lieb F, Moeschler H. 1991. Molecular mode of action of annonins. *Pestic. Sci.* 33:427–38
62. Lowery DT, Isman MB. 1995. Toxicity of neem to natural enemies of aphids. *Phytoparasitica* 23:297–306
63. Marco GJ, Hollingworth RM, Durham W, eds. 1987. *Silent Spring Revisited*. Washington, DC: Am. Chem. Soc. 214 pp.
64. Maistrello L, Henderson G, Laine RA. 2004. Efficacy of vetiver oil and nootkatone as soil barriers against Formosan subterranean termite (Isoptera: Rhinotermitidae). *J. Econ. Entomol.* 94:1532–37
65. McLaughlin JL, Zeng L, Oberlies NJ, Alfonso D, Johnson JA, Cummings BA. 1997. Annonaceous acetogenins as new natural pesticides: recent progress. See Ref. 40, pp. 117–33
66. Mikolajczak KL, McLaughlin JL, Rupprecht JK. 1988. *U.S. Patent No. 4721727*
67. Moeschler HF, Pfuger W, Wendlisch D. 1987. *U.S. Patent No. 4689323*
68. Morse S, Ward A, McNamara N, Denholm I. 2002. Exploring the factors that influence the uptake of botanical insecticides by farmers: a case study of tobacco-based products in Nigeria. *Exp. Agric.* 38:469–79
69. National Research Council. 1992. *Neem. A Tree for Solving Global Problems.* Washington, DC: Natl. Acad. Press. 141 pp.
70. National Research Council. 2000. *The Future Role of Pesticides in US Agriculture.* Washington, DC: Natl. Acad. Press. 301 pp.
71. Naumann K, Isman MB. 1996. Toxicity of neem (*Azadirachta indica* A. uss) seed extracts to larval honeybees and estimation of dangers from field applications. *Am. Bee J.* 136:518–20
72. Perry AS, Yamamoto I, Ishaaya I, Perry RY. 1998. *Insecticides in Agriculture and Environment: Retrospects and Prospects.* Berlin: Springer-Verlag. 261 pp.
73. Pesticide Action Network. 2004. *Pesticide registration by country.* http://www.pesticideinfo.org/Search_Countries.jsp
74. Peterson C, Coats J. 2001. Insect repellents—past, present and future. *Pestic. Outlook* 12:154–58
75. Pittarelli GW, Buta JG, Neal JW Jr, Lusby WR, Waters RM. 1993. *U.S. Patent No. 5260281*
76. Prakash A, Rao J. 1997. *Botanical Pesticides in Agriculture.* Boca Raton, FL: CRC Press. 461 pp.
77. Priestley CM, Williamson EM, Wafford KA, Sattelle DB. 2003. Thymol, a constituent of thyme essential oil, is a positive allosteric modulator of human $GABA_A$ receptors and a homo-oligomeric GABA receptor from *Drosophila melanogaster*. *Br. J. Pharmacol.* 140:1363–72
78. Quarles W. 1996. EPA exempts least-toxic pesticides. *IPM Pract.* 18:16–17
79. Regnault-Roger C, Philogène BJR, Vincent

C, eds. 2005. *Biopesticides of Plant Origin*. Paris: Lavoisier. 313 pp.

80. Rembold H, Mwangi RW. 2002. *Melia volkensii* Gürke. See Ref. 81, pp. 827–32
81. Schmutterer H, ed. 2002. *The Neem Tree*. Mumbai: Neem Found. 892 pp.
82. Shepard HH. 1951. *The Chemistry and Action of Insecticides.* New York: McGraw-Hill. 504 pp.
83. Spollen KM, Isman MB. 1996. Acute and sublethal effects of a neem insecticide on the commercial biocontrol agents *Phytoseiulus persimilis* and *Amblyseius cucumeris* (Acari: Phytoseiidae), and *Aphidoletes aphidimyza* (Rondani) (Diptera: Cecidomyiidae). *J. Econ. Entomol.* 89:1379–86
84. Stroh J, Wan MT, Isman MB, Moul DJ. 1998. Evaluation of the acute toxicity to juvenile Pacific coho salmon and rainbow trout of some plant essential oils, a formulated product, and the carrier. *Bull. Environ. Contam. Toxicol.* 60:923–30
85. Tang JD, Gilboa S, Roush RT, Shelton AM. 1997. Inheritance, stability and lack-of-fitness costs of field-selected resistance to *Bacillus thuringiensis* in diamondback moth (Lepidoptera: Plutellidae) from Florida. *J. Econ. Entomol.* 90:732–41
86. Thacker JMR. 2002. *An Introduction to Arthropod Pest Control*. Cambridge, UK: Cambridge Univ. Press. 343 pp.
87. Trumble JT. 2002. Caveat emptor: safety considerations for natural products used in arthropod control. *Am. Entomol.* 48:7–13
88. Wan MT, Watts RG, Isman MB, Strub R. 1996. An evaluation of the acute toxicity to juvenile Pacific northwest salmon of azadirachtin, neem extract and neem-based products. *Bull. Environ. Contam. Toxicol.* 56:432–39
89. Ware GW. 1883. *Pesticides. Theory and Application.* San Francisco: Freeman. 308 pp.
90. Weinzierl RA. 2000. Botanical insecticides, soaps, and oils. In *Biological and Biotechnological Control of Insect Pests*, ed. JE Rechcigl, NA Rechcigl, pp. 101–21. Boca Raton, FL: CRC Press
91. Zhao JZ, Li YX, Collins HL, Gusukuma-Minuto L, Mau RFL, et al. 2002. Monitoring and characterization of diamondback moth (Lepidoptera: Plutellidae) resistance to spinosad. *J. Econ. Entomol.* 95:430–36

Annual Review of Entomology
Volume 51, 2006

CONTENTS

INDEXES

ERRATA

An online log of corrections to *Annual Review of Entomology* chapters may be found at http://ento.annualreviews.org/errata.shtml