ANNUAL REVIEWS

Annual Review of Entomology

Botanical Insecticides in the Twenty-First Century—Fulfilling Their Promise?

Murray B. Isman

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

Annu. Rev. Entomol. 2020. 65:233–49

First published as a Review in Advance on October 8, 2019

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

https://doi.org/10.1146/annurev-ento-011019-025010

Copyright © 2020 by Annual Reviews.
All rights reserved

ANNUAL REVIEWS CONNECT

www.annualreviews.org

- Download figures
- Navigate cited references
- Keyword search
- Explore related articles
- Share via email or social media

Keywords

pyrethrum, neem, essential oil, pesticide registration, indigenous plants

Abstract

Academic interest in plant natural products with insecticidal properties has continued to grow in the past 20 years, while commercialization of new botanical insecticides and market expansion of existing botanicals has lagged considerably behind. Insecticides based on pyrethrum and neem (azadirachtin) continue to be standard bearers in this class of pesticides, but globally, their increased presence is largely a consequence of introduction into new jurisdictions. Insecticides based on plant essential oils are just beginning to emerge as useful plant protectants. Some countries (such as Turkey, Uruguay, the United Arab Emirates, and Australia) have relaxed regulatory requirements for specific plant extracts and oils, while in North America and the European Union, stricter requirements have slowed progress toward commercialization of new products. Botanicals are likely to remain niche products in many agricultural regions and may have the greatest impact in developing countries in tropical regions where the source plants are readily available and conventional products are both expensive and dangerous to users.

INTRODUCTION

"Perhaps it is time to refocus the attention of the research community toward the development and application of known botanicals rather than to screen more plants and isolate further novel bioactive substances that satisfy our curiosity but are unlikely to be of much utility."

With these words, I concluded a previous review on botanical insecticides for this publication in 2006 (36, p. 62). I reached this conclusion after more than two decades (at the time) of personal research into the discovery and development of botanical insecticides, and because of my increasing recognition that the rate of adoption of this technology was falling well short of the rate of knowledge creation (e.g., scientific publications) in this field. A bibliometric analysis of the scientific literature (41) bore this out; research on botanicals had grown from an insignificant to a substantial proportion (now >20%) of all published insecticide research over a 30-year period beginning in 1980.

In reflecting on the past 15 years since my previous contribution to the *Annual Review of Entomology* (36), I decided against merely reviewing the current scientific state of the art for botanical insecticides at present and decided instead to address two salient questions: (*a*) What have been the (limited) success stories for botanicals in the new millennium, and (*b*) what is impeding their broader implementation and/or commercial success? In short, why have botanicals not lived up to the hype or enthusiasm so prevalent in the 1980s and 1990s? I am taking this particular approach in large part owing to the observation that the science of botanical insecticides (i.e., chemistry, biological activities) has been the subject of numerous reviews in recent years, with unavoidable redundancy (38, 39, 48, 54, 73). In this review, I take an alternative approach because I believe that the limited utilization of botanical insecticides at present is not a consequence of scientific limitations but rather is attributable to other factors.

The impetus for the development of botanical insecticides would appear obvious. In spite of growing evidence of environmental damage and human health concerns, the global use of insecticides has continued to grow over the past 50 years, with explosive growth especially in China and Brazil (30). To be fair, this has partly been accomplished with a shift to newer products with fewer environmental and health impacts; consumers in more affluent countries are increasingly concerned about the safety of the foods that they eat and are applying more pressure on food producers to avoid insecticides that they perceive as imposing health risks; regulatory scrutiny of pesticides has increased worldwide, resulting in fewer products available to growers to mitigate pests (20). This last issue influences growers even in less affluent tropical countries as consumers in affluent temperate countries become more dependent on vegetables, fruits, and other commodities produced in the tropics but demand that these imported commodities meet the same stringent standards as domestic produce. Other pest management sectors that are seeing growing demand for less hazardous products, and for which botanicals may meet part of the demand, include stored product pest management, management of ornamental and landscape plants, control of vectors of human and livestock diseases, management of ectoparasites on companion animals, and management of structural (wood-destroying) pests.

In previous reviews, I highlighted two issues that are especially relevant to the utilization of botanical insecticides: (*a*) The vast majority of pesticide poisonings, and fatalities, worldwide occur in less-developed countries and are attributed to the use of acutely toxic synthetic insecticides (37), and (*b*) there has been a major disconnect between scientific developments in this area and the translation from theory to practice, i.e., implementation of these technologies or products (40). The latter issue emerges as an important theme in this review.

I restrict my discussion to those insect control products derived from terrestrial plants or based on naturally occurring plant chemicals. Microbial insecticides—microorganisms that are infectious in insects or toxic products obtained therefrom—and crop plants themselves that have been modified genetically or through traditional breeding practices to enhance host-plant resistance, are considered to be outside the scope of this review.

I begin by reviewing the major botanical insecticides in current commercial use, then discuss an important avenue through which product formulation can be improved to enhance field performance. This is followed by a discussion of use trends for botanicals in a well-documented jurisdiction—California—and a summary of botanical insecticide approvals in some key countries, providing a global view. I then move to discussing some of the barriers to further implementation of botanicals, present some possible future additions to the arsenal of botanicals, and conclude with my views on the near-term (10–20 year) future for botanicals.

CURRENT COMMERCIAL BOTANICAL INSECTICIDES

Pyrethrum

Commercially successful for at least a century, pyrethrum—obtained from the dried flowers of *Tanacetum cinerariifolium* (Asteraceae)—remains the most widely used botanical insecticide globally, although the exact quantities used are difficult to obtain (21). The production of pyrethrum intended for insecticide production has undergone a major geographical shift in the past 30 years. World production in the twentieth century was dominated by East Africa (principally Kenya and Tanzania at 90% of world production), but political and economic instability in the region created an opportunity seized by entrepreneurs in Australia (Botanical Resources Australia), and by 2009, Tasmania had become the largest growing area and producer of pyrethrum in the world. Efforts to produce pyrethrum in China have been less successful, but Chinese companies and others are trying to revitalize the pyrethrum industry in Kenya (3).

The majority of pyrethrum used in North America and Europe has been for consumer (home and garden) products, for structural pest control, and in public health. The use of pyrethrins for crop protection has grown in recent years; in 2011, over 65% of the pyrethrins used in California were for nonagricultural uses (public health, structural pest control) (18), whereas in 2016, nonagricultural uses accounted for only 52% of all uses (19). This is rather ironic, as the short persistence of such products in field use was the impetus for the discovery and development of synthetic pyrethroids that dominated world insecticide use in the 1980s and 1990s. Another newer and fast-growing application of pyrethrins is in automated misting systems for local management of adult mosquitoes (25).

Neem (Azadirachtin)

Many people credit neem (from *Azadirachta indica*, Meliaceae), and especially its commercial development in the United States and Germany, with revitalizing interest and enthusiasm for botanical insecticides in the 1980s. Indeed research on this plant and its major bioactive constituent, the insect growth regulator azadirachtin, spawned a large number of international conferences, numerous books (e.g., 44, 66, 67), and thousands of research papers (41) (see **Figure 1**).

From the perspective of numbers of countries in which it is approved for use, neem is second only to pyrethrins. Neem-based insecticides are available in many less-developed countries in Africa, the Caribbean, and Latin America, a consequence of the nearly pantropical introduction of neem trees for their provision of shade, use as firewood, and use as a source of natural pharmaceuticals. The ease of seed collection and production of crude seed oil has facilitated their use as insecticides (40). However, in most regions, it has enjoyed limited commercial success, even in its native India, where there is a plethora of registered neem products. The market share for refined

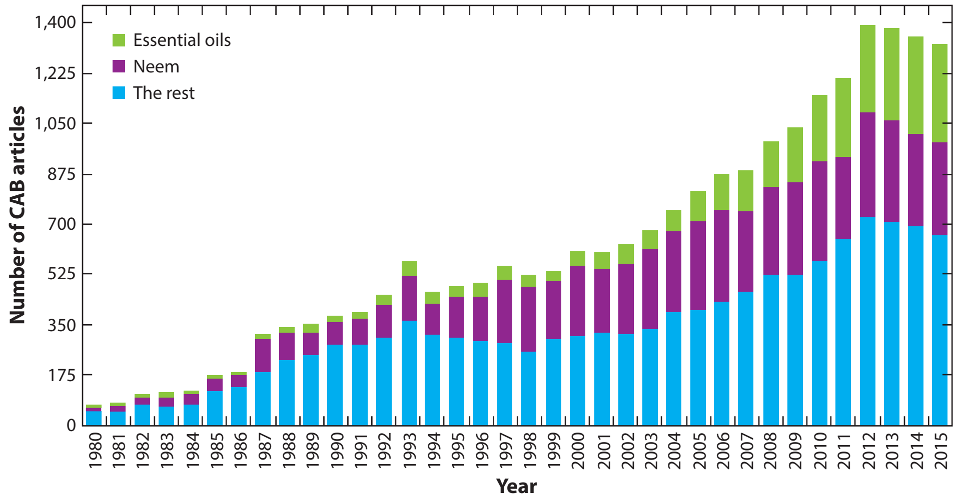

Figure 1

Number of articles in the CAB Abstracts database (Centre for Agriculture and Biosciences International, Wallingford, England) each year from 1980 to 2015. Counts are based on the query: (antifeed* or deterr* or repell* or acaricid* or insecticid* or larvicid*) and (precocene* or neem* or azadiracht* or margosan* or (plant and extract*) or 'essential oil*' or 'botanical insecticid*' or 'plant oil*' or 'vegetable oil*' or derris or 'insecticid* plant*' or 'leaf extract*' or limonoid* or triterpen* or diterpen* or sesquiterpen* or saponin* or terpenoid* or flavonoid*). Figure adapted with permission from Reference 33 (originally adapted from Reference 41), with permission from Elsevier (Cell Press) and the American Chemical Society.

neem extracts, rich in azadirachtin, remains modest in industrialized countries; for example, its use has lagged far behind that of other botanicals in California over the past decade (**Figure 2**). This is in spite of its excellent characteristics—novel mode of action, lack of mammalian toxicity, systemic action in some plants—but probably attributable to its high cost to growers relative to competing products (12, 35). In contrast, clarified neem oil (largely lacking azadirachtin), used as a physical disruptant of pests, has seen large-scale use in the United States, e.g., over 90,000 kg in California in recent years (19).

Essential Oils

Approximately 20 years ago, studies on neem and azadirachtin dominated the scientific literature on botanical insecticides (**Figure 1**). In the past decade, essential oils have challenged and even eclipsed neem as the most popular subject in this field. There are now thousands of published reports of the toxicity of essential oils from particular plants to specific insects, and these have been the subject of several recent reviews (43, 55, 62). Has this tsunami of research effort resulted in a wave of commercial insecticides based on plant essential oils? The answer is a qualified yes. I qualify the answer because a handful of essential oil–based insecticides have recently seen moderate commercial success in North America and Europe, and their markets are expanding to new jurisdictions, especially in Latin America.

Limonene, the major constituent (>90% by weight) of orange oil, is obtained by cold pressing orange skins, ostensibly a byproduct of the citrus industry. Over the past decade, this has been the botanical insecticide most heavily used in California (averaging >20,000 kg per year) (33), with the exception of neem oil (**Table 1**), as noted above. However, more than 90% of limonene (XT2000^{R}) is used in structural pest control (i.e., against wood-destroying termites and ants), although an

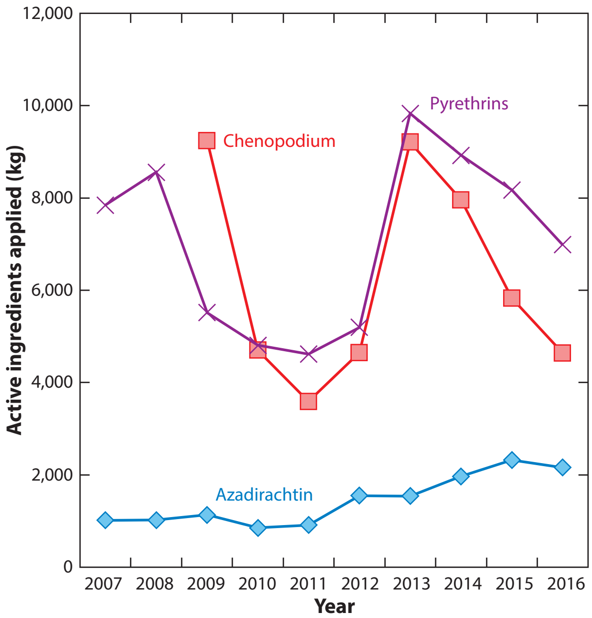

Figure 2

Use of major botanical active ingredients for agricultural pest management in California from 2007 to 2016 (19).

agricultural formulation developed in South Africa (PrevAM[R]) has recently been registered in the United States and the European Union and is beginning to see use on food crops in California.

A plant identified as *Chenopodium ambrosoides* near *ambrosoides* produces an essential oil that was determined to have potential for insect pest management (24). From this oil, a formulated insecticide was developed that became the first new botanical registered in the United States (in 2008) since neem in 1989. Now marketed by Bayer Crop Science as Requiem[R] in North America, this product quickly became the botanical that is most heavily used exclusively for crop protection in California, averaging 8,000 kg of active ingredient per year (19). It is important to point out that the active ingredient in this product is not a naturally occurring essential oil, but rather a blend

Table 1 Use of botanical active ingredients (kg applied) for agricultural insect pest management in California in 2016

Active ingredient	Kg applied
Neem oil (including Margosa oil)	89,928
Chenopodium	4,640
Pyrethrins	3,355
Azadirachtin	2,089
Garlic	385
Orange oil (*d*-limonene)	175
Gerianol or nerolidol	65
Sabadilla	57
Capsicum oleoresin	54

Data taken from Reference 19.

of three synthesized monoterpenoids that are combined to emulate the major constituents of the oil obtained from the plant.

A US company, EcoSMART Technologies, was a pioneer in developing essential oil–based pesticides using Environmental Protection Agency (EPA)-exempt active ingredients (39). Their main agricultural insecticide and miticide, Ecotrol^{TM}, is now produced by KeyPlex and marketed primarily in the United States and Latin America; it is also sold by Brandt under the tradename Ecotec^{TM}. This product, which includes rosemary oil, peppermint oil, and geraniol as active ingredients, is sold in a dozen countries. KeyPlex is currently developing additional terpene-based products for registration in the United States and European Union. While markets for these products are growing at varying paces in different jurisdictions, they have yet to meet the volumes of the botanical products discussed above.

Other Botanicals

Other plant extracts and oils have been successfully commercialized as botanical insecticides. EcoflorAgro in Colombia developed a formulation containing *Capsicum* oleoresin and garlic oil as active ingredients; this product was approved in 2014 by the EPA in the United States under the trade name Captiva^{R}. This and related products from the company are currently registered and sold in 10 countries. In China, some newer commercial insecticides have active ingredients based on matrine and related quinolizidine alkaloids extracted from *Sophora flavescens* (Fabaceae), veratrine and related cevadine-type alkaloids from *Veratrum nigrum* (Melanthiaceae), or celangulin and related dihydroagarofuran sesquiterpenes from *Celastrus angulatus* (Celastraceae). In the United States, McLaughlin Gormley King, the major producer of pyrethrum-based insecticides, has reintroduced an insecticide based on sabadilla alkaloids—Veratran D^{R}—with active ingredient chemistry comparable to that of the veratrine-based botanical in China.

In my previous review of botanicals (36), I noted that acetogenins from *Annona* and related genera (Annonaceae) had been patented for insect control back in the 1980s but, owing to regulatory restrictions, had not been successfully developed into commercial insecticides in North America or Europe. Nonetheless, an insecticide based on seed extracts from the soursop (*Annona squamosa*) and the sweetsop (*Annona reticulata*), containing squamosin as the active ingredient, has been developed in India under the trade name Anosom^{R}. Recent research from Brazil, the geographic center of diversity for the family Annonaceae, pointed to seed extracts from other species with more potent bioactivity that may have potential for the production of botanical insecticides (16, 63).

It is worth noting that two other botanicals that traditionally were among the most widely used for insect control, rotenone and nicotine, have largely fallen out of favor in most industrialized countries (the United States and European Union), at least in crop protection, with China and India as major exceptions to this trend.

OPPORTUNITIES FOR PRODUCT IMPROVEMENT THROUGH FORMULATION

The rapid biodegradation of botanical active ingredients, relative to many synthetics, represents a two-edged sword. It is often cited as a highly desirable property—resulting in few, if any, worker re-entry restrictions; greater compatibility with released biocontrol agents and other natural enemies; and generally greater safety to bees, other pollinators, and other nontarget organisms. In contrast, an oft-cited limitation of botanical insecticides is their lack of persistence on plants under actual field conditions. Most botanicals are highly susceptible to photodegradation (pyrethrins), abiotic oxidation (azadirachtins), or loss through volatilization (essential oil terpenoids) when applied out-of-doors, requiring frequent reapplication of many botanical insecticides when they are used for crop protection (4, 17). In spite of this limitation, certain botanicals have proven track records extending back 2–3 decades, confirming their efficacy in the field (33). Nonetheless, recent developments in formulation chemistry and physics suggest opportunities to dramatically enhance the field performance of botanical insecticides in terms of both efficacy and persistence (28, 64).

A great deal of recent research effort has been directed at the synthesis of green nanoparticles based on plant extracts or oils and metal nanoparticles (12), especially silver (Ag) nanoparticles as mosquito larvicides for control of vector-borne disease (9, 10). Such Ag nanoformulations have included extracts from some seaweed species (50) and numerous terrestrial plants, including extracts from neem (60) and *Annona* (65). In this last-noted study, the nanoformulation increased acute toxicity fourfold to larvae of *Aedes aegypti*, *Anopheles stephensi*, and *Culex quinquefasciatus*, vectors of yellow fever, malaria, and filariasis, respectively. Many of these nanoformulations are effective at very low concentrations (1–30 ppm); while their exact mode of action is as yet unknown, their enhanced efficacy is likely a consequence of their ability to penetrate insect cuticle (11, 68). In addition to their larvicidal action, they effectively deter oviposition by the same vector species at comparable concentrations (14). However, in spite of the promising bioactivities of these materials, none have been commercialized to date. Their effects on aquatic nontarget organisms and possible persistence in aquatic ecosystems may pose a significant obstacle to the use of metal, metal oxide, and carbon nanomaterials from the regulatory perspective (G. Benelli, personal communication), although there are reports indicating that they actually boost predation of mosquito larvae (51), suggesting low toxicity to at least some nontarget species.

Nanoformulation of botanical insecticides using other matrices and carrier systems has also been recently reviewed (28), including encapsulation techniques aimed at providing environmental resilience combined with controlled release of active ingredients. The subject botanicals included in these studies include azadirachtin, rotenone, certain essential oil monoterpenoids, curcumin (from turmeric, *Curcuma longa*) and a large number of essential oils, while the most common matrices include chitosan, cyclodextrins, sodium alginate, zein, and polyethylene glycol. Most of the studies indicate high encapsulation efficiencies (>80%), with strong retention of the bioactive constituents over time, although too few demonstrate pest control efficacy of the prepared formulations.

Da Costa et al. (27) demonstrated that a nanocapsule formulation of azadirachtin lost 20% of the active ingredient after 14 days of UV exposure, whereas unprotected azadirachtin was completely degraded within 7 days. However the nanocapsule formulation was less efficacious than the comparable emulsifiable concentrate formulation against the bean weevil *Zabrotes subfasciatus*, possibly because it limited bioavailability of azadirachtin in the insect. A more positive result was obtained in a study of garlic oil microencapsulated in polyethylene glycol (74). Tested against the red flour beetle *Tribolium castaneum*, garlic oil and a microencapsulated formulation thereof were initially equally efficacious, but efficacy of the oil, applied to milled rice, began to wane after two months. By five months, garlic oil produced only 11% mortality at the highest concentration tested (640 mg/kg rice), whereas the microencapsulated garlic oil produced 80% mortality.

Given the broad bioactivity of essential oils against microorganisms, micro- or nanoencapsulated oils may prove particularly valuable as antimicrobial films for food packaging (e.g., 23) or for application to fresh fruit to prevent or delay postharvest spoilage (e.g., 1). Microemulsions represent yet another formulation option for enhancing bioactivity of essential oils for insect control. A series of microemulsions containing one of three essential oils, or binary mixtures thereof, prepared using Polysorbate 80 were highly toxic to larvae of the mosquito *C. quinquefasciatus*, with LC_{50} values ranging from 1.5 to 4.0 ppm (56). While results such as these are promising, it remains to be seen whether costs and logistics make scaling up of these formulation technologies feasible on a commercial basis.

CURRENT USE TRENDS AND APPROVED PRODUCTS

California

The State of California is a unique jurisdiction in which to examine trends in pesticide use. There are two reasons for this: (*a*) The state produces approximately one-half of all of the fresh fruit and vegetables in the United States, as well as being the dominant source (>50%) of organically certified fruits and vegetables in the country, and (*b*) no other agriculturally rich jurisdiction generates and publishes publicly accessible, detailed (volume by active ingredient and by crop) pesticide use reports on an annual basis (19). Other features of the state are that it produces over 400 agricultural commodities, accounts for >20% of all agricultural pesticide use in the United States, and has a long history of agricultural practices informed and influenced by research at its top-tier academic institutions.

According to 2016 data, and neglecting neem oil, three botanicals saw substantial agricultural use (>1 ton/year): *Chenopodium* (4.6 tons/year), pyrethrins (3.4 tons/year), and azadirachtin (2.1 tons/year) (**Table 1**). As noted above, pyrethrins are also heavily used in structural pest control and for public health (mosquito abatement; management of cockroaches and flies in restaurants, grocery stores, and warehouses), whereas the other two are used almost exclusively for agricultural applications. While azadirachtin use has more than doubled (+212%) over the period from 2007 to 2016, the other two botanicals have not shown any consistent increases in use (**Figure 2**). This relatively flat growth overall stands in contrast to recent estimates that the biopesticide sector is predicted to grow by annual rates of 15–18% (34) or 10–20% (47). Principal reasons for this are that the biopesticide sector is dominated by microbials (e.g., *Bacillus thuringiensis*–based products), and that overall market growth is anticipated to be a response more to introduction of biopesticides into new markets, especially in Latin America, than to an increase in market share in mature markets like California.

Product Approvals in Selected Countries

When I previously explored this subject, few countries included more than a handful of botanical insecticides among their lists of approved products (36). At the time of this writing, there is a wide variation in numbers of approved botanical insecticides among developed countries, ranging from 1 to 2 (Japan, the United Kingdom) to 38 (Korea) (**Table 2**). For the most part, this variation is a consequence of how botanical products are defined within respective countries' regulatory schemes, if indeed they are distinguished from synthetic pesticides at all, and whether some plant extracts or oils are exempt from pesticide registration (as in the United States, Australia). The European Union and its member states are clearly more conservative in this respect than many other jurisdictions (8).

Brazil, China, and India provide striking contrasts in regulatory approval of botanicals, especially in light of the fact that these three countries generate the greatest numbers of published research papers on botanical insecticides (41). No botanicals are fully approved in Brazil at the time of this writing. Ironically, for many years, the Ministry of Agriculture in Brazil has openly promoted the local preparation and use of many plant extracts and oils—including materials such as pyrethrum and neem extracts, approved as pesticides in other countries (38). Until 2019, Brazil had one of the most onerous pesticide regulatory systems in the world. Data review and approval were required by three largely independent government agencies. Recent internal harmonization of pesticide evaluation in Brazil may go some way toward streamlining approval of new products, potentially favoring botanicals and other low-risk products.

India has recently expanded its approved list of botanicals to 11, including several plant oils and extracts. Not surprisingly, a plethora of neem- and azadirachtin-based products dominate

Table 2 Number of botanical AIs approved for use in insect control

Country	AI	Comments and sources
Australia	6	12 EOs are APVMA exempt (**https://apvma.gov.au/node/10831**)
Brazil	0	NA
Canada	6	13 nonconventional pest control products (**https://www.canada.ca/en/health-canada/services/consumer-product-safety/**)
Chile	9	Based on Ministry of Agriculture information (communicated by D. Badulescu)
China	16	NA
European Union	6	Based on EU Pesticides Database information (**http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database**)
France	6	17 natural products (**https://ephy.anses.fr**)
India	11	Based on Government of India information (**http://ppqs.gov.in/divisions/cib-rc/registered-products**)
Japan	1	10 natural safe products (**http://www.acis.famic.go.jp/eng/ailist/index.htm**)
Kenya	3	Biochemical
Korea	38	24 plant extracts, 14 essential oils, based on Ministry of Environment information (communicated by J. Tak)
Mexico	5	Based on Ministry of Agriculture information (communicated by D. Badulescu)
Netherlands	2	5 natural products (**https://pesticidesdatabase.ctgb.nl**)
South Africa	4	NA
United Kingdom	2	Based on Health and Safety Executive information (**http://secure.pesticides.gov.uk/pestreg/**)
United States	13	13 EOs are EPA exempt (**https://www.epa.gov/safepestcontrol/search-registered-pesticide-products**)

Data taken from Reference 34, except where noted. Abbreviations: AI, active ingredient; APVMA, Australian Pesticides and Veterinary Medicines Authority; EO, essential oil; EPA, Environmental Protection Agency; NA, not applicable.

the botanical market in the country that is the native home to the neem tree and from which it was introduced to numerous other tropical and subtropical regions. China has been very active in research on botanical insecticides and is one of the recent global success stories in the development of new commercial botanicals, including some active ingredients (obtained from *Sophora* and *Veratrum*) seeing use in other Asian countries. Korea, another country with a considerable history of research on botanical insecticides, has been quite liberal in approving and promoting the use of a large number of plant extracts and oils for domestic plant protection (J. Tak, personal communication).

BARRIERS TO IMPLEMENTATION OF BOTANICALS

"Regulatory approval remains the most formidable barrier to the commercialization of new botanical insecticides" (36). This statement remains true today. While some jurisdictions have regulatory schemes that are more favorable to approval of plant extracts or oils (e.g., China, Korea), the burden of registration for new botanical insecticides has become increasingly onerous in the United States and the European Union, where it now takes approximately 2 and 4 years, respectively, from data submission to approval. To a large extent, this is a consequence of heightened scrutiny of environmental risks (e.g., to pollinators) rather than stricter interpretation of human health risks. Creating categories intended to expedite approval for low-risk pesticides—variously defined as natural products, natural safe products, biochemical pesticides, or nonconventional products in different countries—has not led to a flood of recent registrations of botanical insecticides and continues to partially stall commercialization (22, 46). It is encouraging, though, that a larger number of small to medium sized companies, including recent startups, are prepared to invest the necessary resources to register new botanicals (47). However, both the United States and Australia have exempted a dozen or more common essential oils—frequently used as flavorings in foods and beverages—for use in insecticide formulations.

Apart from the aforementioned supply-side challenges for pyrethrum in some years, plant biomass has not been a limitation to the production of botanical insecticides to date. However, increasing demand for botanicals—driven by pest resistance to conventional insecticides, regulatory limitations or bans of major products, growth in the organic food sector, and increasing consumer demand for a safe food supply—could reach a point within the next 10–15 years where the available biomass of certain plants is insufficient. For this reason, there is increasing investigation into synthetic routes to natural products, as has already been the case for certain fragrances and flavorings (31, 45). A challenge described above for the production of botanical insecticides—natural chemical variation in plants—can be mitigated through blending of material from multiple sources (40).

FUTURE BOTANICALS

Commercial production of a botanical insecticide depends in part on the sustainable and continuous availability of plant biomass for extraction. Even botanicals produced on a massive scale, notably pyrethrum and neem, have seen production occasionally impeded by supply-side shortages. This is perhaps one reason why so many plant essential oils with potentially useful bioactivity against insects fail to proceed to commercialization—their lack of widespread cultivation.

One rare exception to this might be the essential oil obtained from a selected chemotype of wormwood, *Artemisia absinthium* (Asteraceae). Gonzalez-Coloma and colleagues (7, 32) discovered a chemotype of this well-known plant, the source of the liqueur absinthe, that lacks the toxic and hallucinogenic terpene β-thujone, but produces other novel terpenoids that are toxic and antifeedant to a range of pest insects. EcoflorAgro has invested significant resources toward scaling up cultivation of this plant to secure a supply of the bioactive extract and is pursuing registration (N.C. Duque, personal communication).

The biomass requirement noted above can in some instances be readily met if waste or byproducts of another plant-based industry can be used as feedstock for the extraction of insecticidal compounds. A prime example of this is orange oil, obtained by cold pressing of citrus skins. Acetogenins can likewise be extracted from the seeds of sweetsop and soursop, which are waste products of the juice obtained from those fruits (42).

Recent investigations suggest that byproducts of other plants have the potential to serve as feedstock for the production of future botanical insecticides. Among these plant resources are industrial hemp and other strains of *Cannabis sativa* and *Cannabis indica* (Cannabaceae), which are now being widely cultivated in large part to obtain the medicinal constituent cannabidiol. Benelli and colleagues (15) have demonstrated that crop residue of hemp, i.e., *Cannabis* strains with trivial levels of the hallucinogen Δ9-tetrahydrocannabinol, can generate an essential oil rich in mono- and sesquiterpenes that is toxic to larvae of the southern house mosquito *C. quinquefasciatus*, adult houseflies *Musca domestica*, and the cotton leafworm *Spodoptera littoralis* (see the sidebar titled *Cannabis*—Source and Target). Along similar lines, Pavela and colleagues (59) found that an extract from canes of *Vitis vinifera* cv Cabernet Sauvignon, rich in stilbenes, caused chronic mortality in *S. littoralis*. Given that vine canopy management of wine grapes usually requires annual pruning of canes, the volume of biomass available for extraction from wine-producing regions could be enormous.

CANNABIS—SOURCE AND TARGET

Recent legalization of *Cannabis* in several countries, for both medicinal and recreational use, is resulting in rapidly expanding cultivation of this crop, both in controlled environments and in the field. This has two potentially important implications for botanical insecticides: *Cannabis* can be used (*a*) as a source of biomass for extraction of bioactive substances with potential for use in botanical insecticides (15) and (*b*) as a target crop for application of botanical insecticides with minimal residues and low impact on biocontrol agents. Common pests of cultivated *Cannabis* include rust and spider mites, aphids, and thrips.

THE (NEAR) FUTURE FOR BOTANICAL INSECTICIDES

Recent Successes

In the introduction to this review, I pose two questions: (*a*) What have been the success stories of botanicals in the new millennium, and (*b*) what has impeded their broader implementation? I address the second question in the section titled Barriers to Implementation of Botanicals. Success for botanicals can be measured in multiple ways: (*a*) the number of active ingredients approved for use, (*b*) the number of countries in which a given botanical is approved, and (*c*) the volume of use in a given jurisdiction. Relative to my previous review (36), both the first two of these have shown substantial increases, albeit not at the pace that many proponents had predicted or hoped for. Nonetheless, the recent record suggests a slow march to credibility for botanical insecticides. As noted above, worldwide growth is more likely to be a consequence of introduction of botanicals to new markets (countries) and expansion in crop uses, rather than of simple growth in market share relative to other extant crop protection products. However, fewer conventional products and increasing demand for organic produce will create more opportunity for botanicals to play a role in crop protection.

I also state in the introduction that I have long observed a major disconnect between theory and practice, in this case, between the discovery of insecticidal plant natural products and their commercialization as botanical insecticides. There are obvious reasons why this is the case: (*a*) The cost of discovery research is relatively tiny compared to the overall cost of bringing a new pesticide to market; (*b*) the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization for endemic and indigenous plants adds an additional bureaucratic layer to using plants that private companies may wish to avoid (see the sidebar titled Nagoya Protocol); (*c*) academic and government research institutions

NAGOYA PROTOCOL

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) is a supplement to the multinational Convention on Biological Diversity (**https://www.cbd.int/abs/about**). The main goal of the ABS is to prevent biopiracy—the commercial utilization of a country's nonhuman genetic resources (i.e., plants, animals, microorganisms) by organizations or companies in other countries without prior consent of the country of origin. In effect, the protocol requires that researchers must (*a*) obtain prior consent from a providing country before accessing genetic resources and (*b*) provide a fair and equitable share of the benefits. The latter can be either commercial or noncommercial and can include intellectual property rights. With over 100 signatories, including the European Union, the ABS entered into force in 2014.

pressure scientists into publishing their results, and better scientific journals show preference for novel findings, i.e., findings that make more than incremental contributions to our knowledge; and (*d*) discovering something truly novel is more intellectually satisfying than the laborious task of conducting research moving from proof of concept to practical utility. For these reasons, research on botanical insecticides remains highly skewed toward the discovery end of the R&D spectrum (40). Yet we have seen few botanicals or active principles thereof that match the potent bioactivities or field efficacy of the pyrethrins or azadirachtin.

I have also previously suggested that the greatest impact of botanical insecticides would not be their use in organic crop protection in industrialized agriculture, but rather local, indigenous use in regions such as sub-Saharan Africa where smallholder farmers suffer enormous crop losses pre- and postharvest. These farmers often have limited access to conventional pest-control products and also suffer from pesticide poisonings at a rate far exceeding those in countries with highly developed agriculture (37). In this context, I pointed out that many insecticidal plants that are suitable for use by smallholder farmers are already well known in Africa (40).

Stevenson, Belmain, and colleagues (2, 69–71) have conducted a decade of research aimed at identifying and promoting the use of pesticidal plants in Africa. Much of this work culminated in the publication of a *Handbook on Pesticidal Plants* (5) that, for the 18 most commonly used species, provides botanical descriptions, methods for propagation and cultivation, and methods for simple preparations suitable for crop and postharvest protection. Research and economic development projects with similar objectives could be highly beneficial in tropical and subtropical regions of Asia and South America.

Future Opportunities

Based on what has occurred over the past three decades, it is hard to envision botanicals challenging the dominance of conventional insecticides in highly industrialized crop protection for the foreseeable future, let alone superceding microbial pesticides as the champions of the biopesticide sector. However, botanicals will likely continue to make inroads in market sectors where a premium is placed on human and environmental safety. Examples of these sectors are (*a*) management of domestic and urban pests (e.g., cockroaches, ants, bedbugs) in settings such as schools, hospitals, seniors' homes, restaurants and warehouses; (*b*) management of ectoparasites on food animals and birds, on companion animals (dogs, cats), and for fly control on food animals (poultry, dairy industries); and (*c*) vector control, as in the case of mosquito larvicides and in misting systems aimed at adult mosquitoes (52, 58), and as personal repellents to ticks (see the sidebar titled Tick Repellents). It must be noted that, in many affluent countries, the general public maintains the largely erroneous perception that natural products are inherently safe, in spite of specific examples to the contrary (e.g., nicotine, strychnine) (26, 72). This is an

TICK REPELLENTS

Hard ticks (Acarina: Ixodidae) are important ectoparasites and disease vectors that attack livestock animals, companion animals, and humans directly, in particular as vectors of rickettsias and spirochetes, such as those responsible for Lyme disease. There is a growing body of scientific evidence that botanicals can be acaricidal to ticks; among these, essential oils may be particularly effective as personal repellents for humans (13, 57, 61). This is an example of a specific pest management sector where botanicals could prove to be as or more effective than conventional, synthetic products.

argument in favor of continued regulatory scrutiny of botanical insecticides, even where the data requirements are somewhat reduced relative to synthetic pesticides.

In agriculture, botanicals are gaining favor in organic food production but are also earning a place in conventional farming as participants in pesticide rotations or as tank mixes in cases where the use of conventional products can be reduced without loss of efficacy or increased cost. There is emerging evidence that some plant essential oils can synergize the toxicity of certain conventional insecticides (6, 29, 53). While laboratory studies indicate that botanicals can have negative impacts on natural enemies or biocontrol agents (49), field studies suggest that botanicals can be efficacious against pests while conserving beneficial arthropods (71). Botanicals should also play an increasingly recognized role as crop protectants in controlled environments, i.e., in greenhouse and indoor cultivation of food and medicinal crops, where biological control is often the dominant pest management practice, but where spot treatment of infestations or pest removal immediately prior to harvest is frequently a necessity.

Undoubtedly, there will be specific sectors, crops, contexts, or regions where botanicals will prove to be especially effective and will emerge as key components of insect pest management. For this to be optimally achieved, improvements to enhance formulations and more conscientious efforts to educate farmers on the modes of action and nontoxic behavioral effects of botanicals will continue to be required.

SUMMARY POINTS

1. Recent success in commercialization of new botanical insecticides is somewhat disappointing when viewed against the rapidly growing scientific literature on the subject.
2. Growth in the use of botanical insecticides is more a consequence of introduction to new markets (countries) than of growing market share in mature agricultural markets.
3. Regulatory approval remains the greatest barrier to implementation of botanical insecticides, especially in the United States and European Union, although certain other countries are more favorably disposed to the use of plant extracts and oils.
4. Nanoparticle and nanoemulsion formulations can enhance bioactivity and efficacy of plant natural products; such formulations may prove useful as mosquito larvicides for vector control and in other pest management contexts.
5. There may be major opportunities for botanicals in public health and urban pest management and as crop protectants for medicinal and food crops grown in controlled environments.
6. Globally, the greatest benefits of botanical insecticides may accrue to smallholder farmers in developing countries.

FUTURE ISSUES

1. Compatibility and/or synergy of botanical insecticides with conventional microbial and mineral-based insecticides merits further attention, especially as long-used conventional products are displaced by loss of regulatory status and insecticide resistance.
2. Botanicals as mosquito larvicides require more comprehensive demonstrations of field efficacy and safety to aquatic ecosystems.

3. Better demonstration and understanding of the contribution of behavioral effects (feeding, oviposition deterrence, repellence) to crop protection efficacy under field conditions are needed.
4. Swifter progress toward harmonization of regulatory standards across major jurisdictions is needed to facilitate the introduction of more biopesticides.

DISCLOSURE STATEMENT

For two decades, the author conducted research for EcoSMART Technologies and KeyPlex, a US producer of botanical insecticides. He also consults for biopesticide companies in Canada, Australia, and the United Kingdom.

ACKNOWLEDGMENTS

I thank numerous industry and research colleagues and collaborators for sharing their insights and directing me to additional information sources.

LITERATURE CITED

1. Aloui H, Khwaldia K, Licciardello F, Mazzaglia A, Muratore G, et al. 2014. Efficacy of the combined application of chitosan and locust bean gum with different citrus essential oils to control postharvest spoilage caused by *Aspergillus flavus* in dates. *Int. J. Food Microbiol.* 170:21–28
2. Amoabeng BW, Gurr GM, Gitau CW, Stevenson PC. 2014. Cost:benefit analysis of botanical insecticide use in cabbage: implications for smallholder farmers in developing countries. *Crop Protect*. 57:71–76
3. Andae G. 2017. China firm among four to invest in pyrethrum sector. *Bus. Daily*, June 26. **https://www.businessdailyafrica.com/markets/marketnews/China-firm-among-four-to-invest-in-pyrethrum-sector/3815534-3988444-xtiabez/index.html**
4. Angioni A, Dedola F, Minello EV, Barra A, Cabras P, Caboni P. 2005. Residues and half-life times of pyrethrins on peaches after field treatments. *J. Agric. Food Chem.* 53:4059–63
5. **Anjarwalla P, Belmain S, Sola P, Jamnadass R, Stevenson PC. 2016. *Handbook on Pesticidal Plants*. Nairobi, Kenya: World Agrofor. Cent. (ICRAF)**

5. Handy guide to cultivation and preparation of plants for pest management in Africa.

6. Arena JS, Omarini AB, Zunino MP, Peschiutta ML, Defago MF, Zygadlo JA. 2019. Essential oils from *Dysphania ambrosioides* and *Tagetes minuta* enhance the toxicity of a conventional insecticide against *Alphitobius diaperinus*. *Indust. Crops Prod.* 122:190–94
7. Bailen M, Julio JF, Diaz CE, Sanz J, Martinez-Diaz RA, et al. 2013. Chemical composition and biological effects of essential oils from *Artemisia absinthium* L. cultivated under different environmental conditions. *Indust. Crops Prod.* 49:102–7
8. **Balog A, Hartel T, Loxdale HD, Wilson K. 2017. Differences in the progress of the biopesticide revolution between the EU and other major crop-growing regions. *Pest Manag. Sci.* 73:2203–8**

8. Highlights the issue of strict regulatory requirements in industrialized countries.

9. Benelli G. 2016. Green synthesized nanoparticles in the fight against mosquito-borne diseases and cancer—a brief review. *Enzyme Microb. Technol.* 95:58–68
10. Benelli G. 2016. Plant-mediated biosynthesis of nanoparticles as an emerging tool against mosquitoes of medical and veterinary importance: a review. *Parasitol. Res.* 115:23–34
11. Benelli G. 2018. Mode of action of nanoparticles against insects. *Environ. Sci. Pollut. Res.* 25:12329–41
12. Benelli G, Canale A, Toniolo C, Higuchi A, Murugan K, et al. 2016. Neem (*Azadirachta indica*): towards the ideal insecticide? *Nat. Prod. Res.* 31:a369–86
13. Benelli G, Pavela R, Canale A, Mehlhorn H. 2016. Tick repellents and acaricides of botanical origin: a green roadmap to control tick-borne diseases? *Parasitol. Res.* 115:2545–60

14. Benelli G, Pavela R, Maggi F, Petrelli R, Nicoletti M. 2017. Commentary: making green pesticides greener? The potential of plant products for nanosynthesis and pest control. *J. Clust. Sci.* 28:3–10

15. Benelli G, Pavela R, Lupidi G, Nabissi M, Perelli R, et al. 2018. The crop-residue of fiber hemp cv. Futura 75: from a waste product to a source of botanical insecticides. *Environ. Sci. Pollut. Res.* 25:10515–25
16. Bernardi D, Ribeiro L, Andreazza F, Neitzke C, Oliveira EE, et al. 2017. Potential use of *Annona* byproducts to control *Drosophila suzukii* and toxicity of its parasitoid *Trichopria anastrephae*. *Indust. Crops Prod.* 110:30–35
17. 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
18. Calif. Dept. Pestic. Regul. 2011. *Summary of pesticide use report data 2011, indexed by chemical*. Rep., Calif. Dept. Pestic. Regul., Sacramento
19. Calif. Dept. Pestic. Regul. 2016. *Summary of pesticide use report data 2016, indexed by chemical*. Rep., Calif. Dept. Pestic. Regul., Sacramento
20. Carvhalo FP. 2017. Pesticides, environment, and food safety. *Food Energy Sec.* 6:48–60
21. Casida JE, Quistad GB. 1995. *Pyrethrum Flowers: Production, Chemistry, Toxicology and Uses*. Oxford, UK: Oxford Univ. Press
22. Chandler D, Bailey AS, Tatchell GM, Davidson G, Greaves J, Granta WP. 2011. The development, regulation and use of biopesticides for integrated pest management. *Phil. Trans. R. Soc. B* 366:1987–98
23. Chen H, Li L, Ma Y, McDonald TP, Wang Y. 2019. Development of active packaging film containing bioactive components encapsulated in β-cyclodextrin and its application. *Food Hydrocoll.* 90:360–66
24. Chiasson H, Vincent C, Bostanian NJ. 2004. Insecticidal properties of a *Chenopodium*-based botanical. *J. Econ. Entomol.* 97:1378–83
25. Cilek JE, Mulrennan JA Sr. 2008. Evaluation of an automatic-timed insecticide application system for backyard mosquito control. *J. Am. Mosq. Control Assoc.* 24:560–5
26. Coats JR. 1994. Risks from natural versus synthetic insecticides. *Annu. Rev. Entomol.* 39:489–515
27. Da Costa JT, Forim MR, Costa ES, De Souza JR, Mondego JM, Boica AL Jr. 2014. Effects of different formulations of neem oil-based products on control *Zabrotes subfasciatus* (Boheman, 1833) (Coleoptera: Bruchidae) on beans. *J. Stored Prod. Res.* 56:49–53
28. De Oliveira JL, Ramos Campos EV, Bakshi M, Abhilash PC, Fraceto LF. 2014. Application of nanotechnology for the encapsulation of botanical insecticides for sustainable agriculture: prospects and promises. *Biotechnol. Adv.* 32:1550–61
29. Faraone N, Hillier NK, Cutler GC. 2015. Plant essential oils synergize and antagonize toxicity of different conventional insecticides against *Myzus persicae* (Hemiptera: Aphididae). *PLOS ONE* 10(5):e0127774
30. Food Agric. Org. 2017. *Pesticide use, tonnes*. Rep., Food Agric. Org., U.N., New York. **https://ourworldindata.org/grapher/pesticide-use-tonnes?time=1990..2014**
31. Forti L, Di Mauro S, Cramarossa MR, Filippucci S, Turchetti B, Buzzini P. 2015. Non-conventional yeast whole cells as efficient biocatalysts for the production of flavors and fragrances. *Molecules* 20:10377–98

32. Gonzalez-Coloma A, Bailen M, Diaz CE, Fraga B, Martinez-Diaz R, et al. 2013. Major components of Spanish cultivated *Artemisia absinthium* populations: antifeedant, antiparasitic, and antioxidant effects. *Indust. Crops Prod.* 37:401–7

33. Grieneisen MJ, Isman MB. 2018. Recent developments in the registration and usage of botanical pesticides in California. In *Managing and Analyzing Pesticide Use Data for Pest Management, Environmental Monitoring, Public Health, and Public Policy*, ed. M Zhang, S Jackson, MA Robertson, MR Zeiss, pp. 149–69. Washington, DC: Am. Chem. Soc.
34. Guest P. 2018. *Global Biopesticide Regulations 2018. Legislation and Administration; Registration Process; Regulatory Challenges; Registered Products; Support Initiatives*. London, UK: Informa UK Ltd.
35. Isman MB. 2004. Factors limiting commercial success of neem insecticides in North America and Western Europe. In *Neem: Today and in the New Millenium*, ed. O Koul, S Wahab, pp. 33–41. Dordrecht, Neth.: Kluwer
36. Isman MB. 2006. Botanical insecticides, deterrents, and repellents in modern agriculture and an increasingly regulated world. *Annu. Rev. Entomol.* 51:45–66

14. Comprehensive review of the emerging field of green nanoformulations.

32. Good example of basic plant science creating a foundation for new botanical products.

37. Isman MB. 2008. Botanical insecticides: for richer, for poorer. *Pest Manag. Sci.* 64:8–11
38. Isman MB. 2014. Botanical insecticides: a global perspective. In *Biopesticides: State of the Art and Future Opportunities*, ed. AD Gross, JR Coats, SO Duke, JN Seiber, pp. 21–30. Washington, DC: Am. Chem. Soc.
39. Isman MB. 2015. A renaissance for botanical insecticides? *Pest Manag. Sci.* 71:1587–90
40. **Isman MB. 2017. Bridging the gap: moving botanical insecticides from the laboratory to the farm. *Indust. Crops Prod.* 110:10–14**

40. Expands on the opportunities to develop and use botanical insecticides in developing countries.

41. Isman MB, Grieneisen MJ. 2014. Botanical insecticide research: many publications, limited useful data. *Trends Plant Sci*. 19:140–45
42. Isman MB, Seffrin R. 2014. Natural insecticides from the Annonaceae: a unique example for developing biopesticides. In *Advances in Plant Biopesticides*, ed. D Singh, pp. 21–33. Berlin: Springer
43. Isman MB, Tak J-H. 2017. Commercialization of insecticides based on plant essential oils: past, present, and future. In *Green Pesticides Handbook: Essential Oils for Pest Control*, ed. LML Nollet, HS Rathore, pp. 27–39. Boca Raton, FL: CRC Press
44. Koul O, Wahab S, eds. 2004. *Neem: Today and in the New Millennium*. Dordrecht, Neth.: Kluwer
45. Leavell MD, McPhee DJ, Paddon CJ. 2016. Developing fermentative terpenoid production for commercial usage. *Curr. Opin. Biotechnol.* 37:114–19
46. Marchand PA. 2015. Basic substances: an opportunity for approval of low-concern substances under EU pesticide regulation. *Pest Manag. Sci.* 71:1197–200
47. Marrone PG. 2019. Pesticidal natural products: status and future potential. *Pest Manag. Sci.* 75. In press
48. Miresmailli S, Isman MB. 2014. Botanical insecticides inspired by plant-herbivore chemical interactions. *Trends Plant Sci*. 19:29–35
49. Monsreall-Ceballos RJ, Ruiz-Sanchez E, Ballina-Gomez HS, Reyes-Ramirez A, Gonzalez-Moreno A. 2018. Effects of botanical insecticides on hymenopteran parasitoids: a meta-analysis approach. *Neotrop. Entomol.* 47:681–88
50. Murugan K, Benelli G, Ayyappan S, Dinesh D, Panneerselvam C, et al. 2015. Toxicity of seaweed-synthesized silver nanoparticles against the filariasis vector *Culex quinquefasciatus* and its impact on predatory efficiency of the cyclopoid crustacean *Mesocyclops longisetus*. *Parasitol. Res*. 14:2243–53
51. Murugan K, Benelli G, Panneerselvam C, Subramaniam J, Jeyalalitha T, et al. 2015. *Cymbopogon citratus*-synthesized gold nanoparticles boost the predation efficiency of copepod *Mesocyclops aspericornis* against malaria and dengue mosquitoes. *Exp. Parasitol.* 153:129–38
52. Norris EJ, Bartholomay L, Coats JR. 2018. Present and future outlook: the potential of green chemistry in vector control. In *Advances in the Biorational Control of Medical and Veterinary Pests*, ed. EJ Norris, JR Coats, AD Gross, JM Clark, pp. 43–62. Washington, DC: Am. Chem. Soc.
53. **Norris EJ, Johnson JB, Gross AD, Bartholomay LC, Coats JR. 2018. Plant essential oils enhance diverse pyrethroids against multiple strains of mosquitoes and inhibit detoxification enzyme processes. *Insects* 9:132**

53. Comprehensive study on synergy of pyrethroids by essential oils.

54. Pavela R. 2016. History, presence and perspective of using plant extracts as commercial botanical insecticides and farm products for protection against insects: a review. *Plant Protect. Sci.* 52:229–41
55. Pavela R, Benelli G. 2016. Essential oils as ecofriendly biopesticides? Challenges and constraints. *Trends Plant Sci*. 21:1000–7
56. Pavela R, Benelli G, Pavoni L, Bonacucina G, Cespi M, et al. 2019. Microemulsions for delivery of Apiaceae essential oils: towards highly effective and eco-friendly mosquito larvicides? *Indust. Crops Prod.* 129:631–40
57. Pavela R, Canale A, Mehlhorn H, Benelli G. 2016. Application of ethnobotanical repellents and acaricides in prevention, control and management of livestock ticks: a review. *Res. Vet. Sci.* 109:1–9
58. Pavela R, Maggi F, Iannarelli R, Benelli G. 2019. Plant extracts for developing mosquito larvicides: from laboratory to field, with insights on the modes of action. *Acta Tropica* 193:236–71
59. **Pavela R, Waffo-Tegno P, Blais B, Richard T, Merillon J-M. 2017. *Vitis vinifera* canes, a source of stilbenoids against *Spodoptera littoralis* larvae. *J. Pest Sci.* 90:961–70**

59. Interesting example of plant waste material as potential feedstock for a new botanical insecticide.

60. Poopathi S, De Britto LJ, Praba VL, Mani C, Praveen M. 2015. Synthesis of silver nanoparticles from *Azadirachta indica*: a most effective method for mosquito control. *Environ. Sci. Pollut. Res.* 22:2956–63

61. Rand PW, Lacombe EH, Elias SP, Lubelczyk CB, St Amand T, Smith RP Jr. 2010. Trial of a minimal-risk botanical compound to control the vector tick of Lyme disease. *J. Med. Entomol.* 47:695–98
62. Regnault-Roger C, Vincent C, Arnason JT. 2012. Essential oils in insect control: low-risk products in a high-stakes world. *Annu. Rev. Entomol.* 57:405–25
63. Ribeiro LP, Akhtar Y, Vendramim JD, Isman MB. 2015. Comparative bioactivity of selected seed extracts from Brazilian *Annona* species and an acetogenin-based commercial bioinsecticide against *Trichoplusia ni* and *Myzus persicae*. *Crop. Protect*. 62:100–6
64. Sahayaraj K. 2014. Nanotechnology and plant biopesticides: an overview. In *Advances in Plant Biopesticides*, ed. D Singh, pp. 279–93. Berlin: Springer
65. Santhosh SB, Yuvarajan R, Natarajan D. 2015. *Annona muricata* leaf extract-mediated silver nanoparticles synthesis and its larvicidal potential against dengue, malaria and filariasis vector. *Parasitol. Res.* 114:3087–96
66. Schmutterer H. 1990. Properties and potential of natural pesticides from the neem tree, *Azadirachta indica*. *Annu. Rev. Entomol.* 35:271–97
67. Schmutterer H, ed. 2002. *The Neem Tree*. Mumbai: Neem Found. 2nd ed.
68. **Shahzad K, Manzoor F. 2019. Nanoformulations and their mode of action in insects: a review of biological interactions. *Drug Chem. Toxicol.* 42. In press**

68. Thorough review of effects of nanoparticles in insects.

69. Sola P, Mvumi BM, Nyirenda SPM, Ogendo JO, Mponda O, et al. 2014. Botanical pesticide production, trade and regulatory mechanisms in sub-Saharan Africa: making a case for plant-based pesticidal products. *Food Sec*. 6:369–84
70. Stevenson PC, Isman MB, Belmain SR. 2017. Pesticidal plants in Africa: a global vision of new biological control products from local uses. *Indust. Crops Prod.* 110:2–9
71. **Tembo Y, Mkindi AG, Mkenda PA, Mpumi N, Mwanauta R, et al. 2018. Pesticidal plant extracts improve yield and reduce insect pests on legume crops without harming beneficial arthopods. *Front. Plant Sci.* 9:1425**

71. Good field demonstration of compatibility of botanical insecticides with natural enemies.

72. Trumble JT. 2002. Caveat emptor: safety considerations for natural products used in arthropod control. *Am. Entomol.* 48:7–13
73. Walia S, Saha S, Tripathi V, Sharma KK. 2017. Phytochemical biopesticides: some recent developments. *Phytochem. Rev.* 16:989–1007
74. Yang F-L, Li X-G, Zhu F, Lei C-L. 2009. Structural characterization of nanoparticles loaded with garlic essential oil and their insecticidal activity against *Tribolium castaneum* (Herbst) (Coleoptera: Tenebrionidae). *J. Agric. Food Chem.* 57:10156–62