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REVIEW

Pest management with biopesticides

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Abstract Biopesticides are attracting interest as alternatives to conventional pesticides but without many of the non-target effects, promising a better record of safety and sustainability in pest control practices. In this article we summarize and discuss the current status and future promise of biopesticides, including how biopesticides use may increase the quality and safety of the food supply.

Keywords biopesticide, GMO crops, pest management

1 Introduction

Pesticides may be defined as chemicals (or mixtures of chemicals) used to restrict or repel pests such as insects, weeds, fungi, nematodes, and other organisms that adversely affect food production, ecosystem function or human health. Pesticides may also be toxic contaminants in our food supply and environment (air, water, soil), and responsible for illness or injury to people and wildlife. Biopesticides are attracting interest as alternatives to conventional pesticides, but without many of the non-target effects, by offering improved safety in pest control practices. In this manuscript, we summarize and discuss the current status and future promise of biopesticides, including in China and other developing agricultural economies, and how biopesticides use may increase the safety and sustainability of the food supply.

2 Current trends

Pesticide use in California and the US peaked in the early 1980s. Since then there has been a trend toward less pesticide use[1]. This trend reflects a combination of several factors: the banning or phase-out of high volume use synthetics, like toxaphene, chlordane, and methyl bromide; development of more efficient application technology which delivers more chemical to the target and allows less chemical loss by volatilization and wind erosion, to soil, and by surface runoff; and the introduction of transgenic modifications in some crops like cotton, corn, and soybeans so that resistance to pests or tolerance is carried by the crop without need for, or minimal use of, external chemical application for pest control. An example is the technology underlying the use of transgenic *Bacillus thuringiensis* (*Bt*) toxin to control insects. Farmers are also using more integrated pest management tools such as intercropping, cover crops, biocontrol, and crop rotation, along with reduced risk chemicals such as synthetic pyrethroids, avermectins, and spinosads that are generally effective at lower application rates than conventional pesticides[2].These tools all work to reduce the amount of chemical applied to crops to obtain economically acceptable levels of pest control. They will also improve the safety of food production by eliminating or minimizing the use of costly chemicals that leave toxic residues in foods, or lead to illness in farm worker populations, and do so at lower costs in many cases.

2.1 Biopesticides

"Biopesticides" would be all of these things included in the definition of pesticides but with several modifications, in particular that they are naturally occurring or derived from natural products by straightforward chemical modification. The EPA definition is that biopesticides are natural compounds or mixtures that manage pests without a toxic mode of action, such as cholinesterase inhibition which is a characteristic of most organophosphate and carbamate insecticides[3].

Third generation pest control agents, reduced risk pesticides, and biobased pesticides are other terms sometimes used in place of "biopesticides". The common elements of biopesticides can include some or all of the

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following: naturally occurring, reduced toxicity to non-target organisms, low persistence in the environment or in ecological food chains, compatibility with organic farming methods, and low mammalian toxicity so that they are safe to handle, and not restricted in use by regulatory agencies[4,5]. Few products will fit all of these criteria, but the intent is clearly to stimulate 'green' environmentally benign technologies for sustainable pest management and control.

Although the market is growing for biopesticides, none of the top-use pesticides in recent years in California or the US clearly meet the biopesticide definition[1]. One could argue that sulfur is close, since it is naturally occurring and of low non-target toxicity, and useable in organic farming, but sulfur has been used for pest control for centuries and is not among the new generation of pest control agents[6]. Furthermore, sulfur must be refined from its natural sources in the environment before it can be marketed and sold for use as a pesticide. Various mineral oils used for weed control, some plant essential oils (e.g., orange oil for termite control), and corn gluten for weed control might be considered within the realm of biopesticides as well.

Spinosads well represent the commercial possibilities for biopesticides, recently gaining a large market share for protection of apples, pears, strawberries and other high-value crops. In part this is because the residues left by spinosads are of low toxicity, and product is considered safe for consumers, including infants and children, when the product is applied in the manner specified on the label, and are approved in the US for organic production. Spinosyns — there are two active forms, A and D differing only by placement of a methyl group (Fig. 1) — are produced by soil-borne fungi (*Saccharopolyspora spinosa*) which can also be used in fermentation culture to produce the technical product. The use of fermentation to produce chemical control agents is another potential advantage for biopesticides since it can reduce or eliminate the need for extensive chemical processing facilities associated with pesticides based on petrochemicals.

In addition to Dow's spinosads, Merck and other firms have developed avermectins (Fig. 1), macrocyclic lactones produced by fermentation of naturally-occurring soil bacteria (*Streptomyces avermitilis*) which are useful for crop protection as well as treatment of livestock and pets for parasite and disease control.

A number of specialty pesticide companies, like Trécé, Certis USA, and Marrone Bio Innovations (Table 1) have marketed new biopesticides, and now larger companies like Monsanto, DuPont, Bayer, BASF, and Dow are developing and/or marketing biopesticides along with conventional (2nd generation) pest control chemicals. EPA has helped to move the biopesticide technology forward by offering a "fast-track" for registration of reduced toxicity pesticides. The newer bioproducts include fungicides, insect repellants and attractants (semiochemicals), insecticides, nematicides, herbicides and products from genetic manipulation. In China, India, and several other developing economies, technologies for pest control are being developed based upon farmers experience in those countries. In the Philippines, for example, rice can be grown along with Tilapia in the paddies. The tilapia fish consume insect pests of rice, so that no chemical control may be needed, and then become a nutritious co-product harvestable along with the rice crop.

Bioherbicides are a future target for development, although research in this area has been somewhat slow since the last new mode of action herbicides were introduced more than 20 years ago[7].The evolution of weeds resistant to the leading herbicide glyphosate may accelerate developments in this area[8]. Non-synthetic chemical management of weeds in organic culture is a serious problem limiting wider use of organic farming methods. The few bio- or green-products for weed control use high application rates or multiple applications, and even then are somewhat unpredictable in efficacy[9]. Mechanical control methods include hoeing, mowing, burning, or solarization under plastic tarps, as well as use of grazing sheep and goats. Many of these methods are laborious, costly, and often unreliable, or accompanied by undesirable environmental side effects.

The development of the new triketone herbicides is a case in point, where observation of herbicidal activity from an ornamental plant (bottlebrush), led to the isolation of the naturally occurring bioactive principle, leptospermone, and various synthetic analogs that are now commercial herbicides, such as mesotrione (Fig. 1). Mesotrione was brought to market by Syngenta in 2001. It is a synthetic analog of leptospermone which mimics the herbicidal effects of this natural product[10]. It is a member of the class of HPPD inhibitors which work by inhibiting 4-hydroxyphenylpyruvate dioxygenase. HPPD is required by plants for carotenoid and plastoquinone biosynthesis; carotenoids protect chlorophyll from sunlight-induced degradation and plastoquinone is required for photosynthesis. When the HDDP inhibitor is present in plants, carotenoids are prevented from being made and photosynthesis is inhibited, causing chlorophyll to degrade, followed by plant death. Sales by Syngenta were more than 400 million USD per year in 2011, but expiration of patents beginning in 2012 has opened the market to other synthetic triketone herbicides[11].

Another future major market to be addressed is for bionematicides for soil application and use in stored products, given the mandated (Montreal Protocol[12]) phaseout of methyl bromide, and off-target movement and exposure issues with present fumigants like methyl isothiocyanate (MITC), formed from synthetic metam products, and chloropicrin. Avermectins show some promise for nematode control, particularly in combination with other control measures, and farmers are adopting

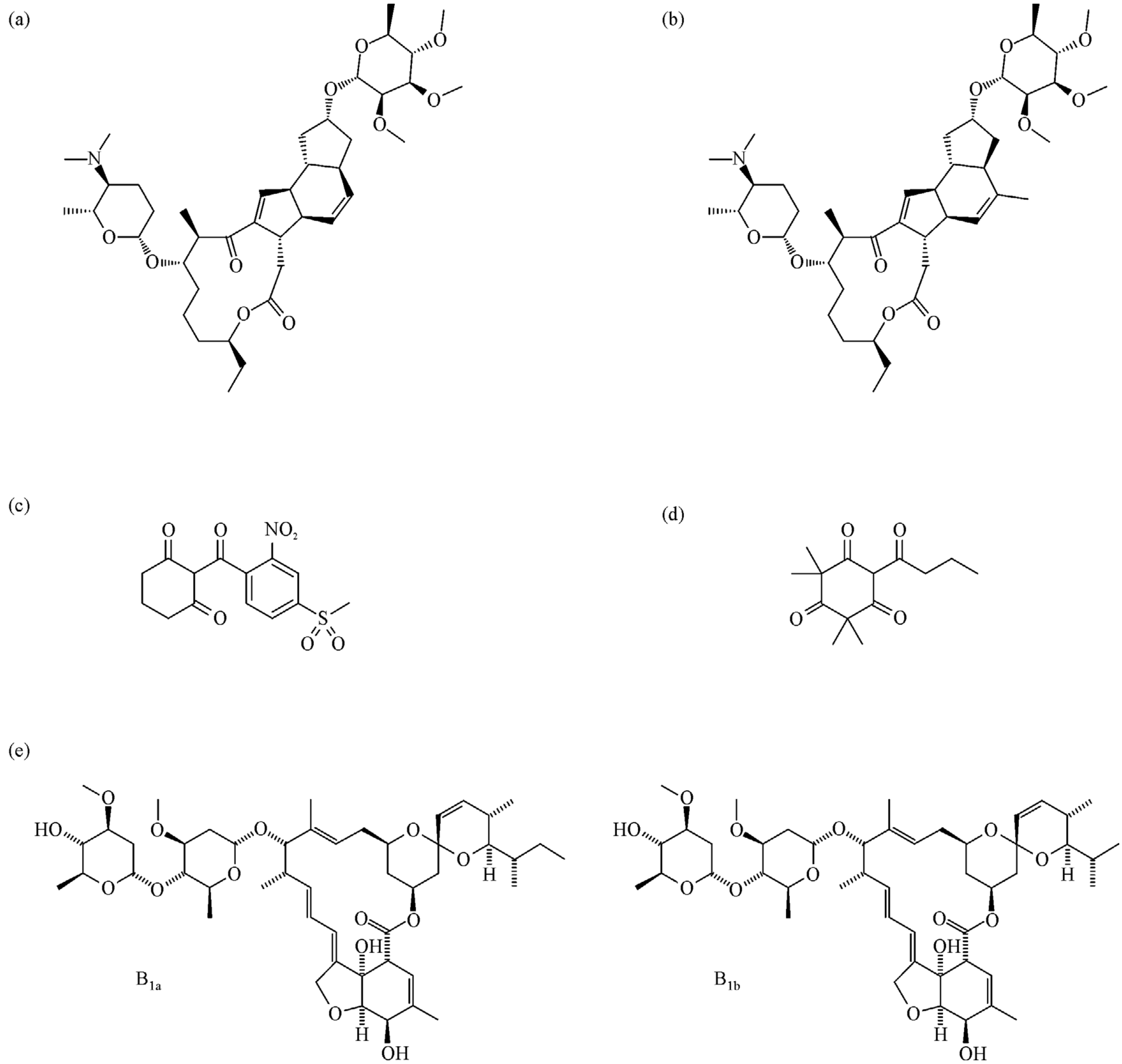

Fig. 1 Structures of some biopesticide or biopesticide derivative. (a) Spinosyn A; (b) spinosyn D; (c) mesotrione; (d) leptospermone; (e) avermectins. Structure source: Wikipedia, accessed on Oct. 17, 2017.

cultural methods (crop rotation, intercropping with *Brassica* species, solarization, etc) to address nematodes in the more susceptible crops like strawberries and carrots.

There is renewed interest in discovering botanical and related pesticides with novel structures and activity that can be used directly, or to inspire synthetic modification to form the pest control agents of the future. As Isman and others[13,14] have pointed out, plants produce a bewildering array of “secondary metabolites” thought to play an ecological role in defending plants from attack by herbivores and pathogens, as well in chemically inhibiting competing plant species. These range from the familiar biopesticides of long standing interest, such as pyrethrins, rotenones, and alkaloids, to complex mixtures of terpenes, carbohydrates and proteins. Natural pesticide discovery is particularly pursued in Asia and Latin America as a way to overcome costly regulatory requirements in industrialized nations. The products are often complex unrefined mixtures of active ingredients and other components of presently unknown utility to the source plant or microbes.

Pesticide discovery has experienced renewed interest ranging from exploration of plants and microbes that produce chemicals and mixtures of potential utility to mainstream agriculture, to niche products that can be exploited by synthetic and biotechnological modifications in the future. There are plenty of areas yet to explore, by chemical synthesis, biotechnology, breeding, and by ecosystem scientists and engineers. The success of the

Table 1 Examples of biopesticides marketed by specialty and major crop protection companies

Biopesticide	Company	Use	Type
Spinosad	Dow	Insecticides	Spinosoids, spinosyns A and D
Avermectins	Merck and others	Anthelmintics, insecticides	Macrocyclic lactones
Serenade, Requiem, Sonata, Ballad	Bayer crop science	Insecticides, fungicides	Microbial strains and mixtures
Cidetrak	Trécé	Insect control via mating disruption; gustatory stimulation coupled with an insecticide	Pheromones, kairomones
Venerate, Grandevo, Majestene	Marrone Bio Innovations	Insecticides, acaricides, nematicides	Microbial strains and mixtures
PFR-97, CYD-X, Gemstar, etc.	Certis USA	Insecticides, miticides	Insecticidal microbes and viruses

current group of biopesticides will likely be expanded as more scientists and practitioners are attracted to the critically important field of pest control in sustainable food production.

2.2 Other alternatives to pesticides

The excitement over biopesticides, semiochemical communication cues, and other alternative controls, which was evident in the 1970s when the 3rd generation pest control movement was launched[15], is now regaining momentum. Over half of the new registrations for pesticides and pest control agents at EPA are for products associated with the features of biopesticides, and the market share is growing for these products[4].

High throughput screening methods, nano-based encapsulation methods, and further development of semiochemicals for both monitoring and population control of pests offer promise for further developments. Semiochemicals are already far along in crop protection applications. Pheromones or synthetic analogs are widely used to survey for pest populations, so that insecticide applications can be timed and positioned to be most effective. Mass trapping or confusion approaches have also been used with some success, using pheromones or synthetic or naturally occurring alternatives that disrupt pest insect populations. An example is the pheromone and a naturally occurring alternative with pheromone-like attractant activity found in pear leaves that can aid in control of codling moth in apple, pear, walnut, almond, and other crops susceptible to economic damage by codling moth[16]. Controlling this damaging pest, and other boring insects that affect cotton seed and peanuts, is a critical element in controlling invasion of *Aspergillus* fungi, which can affect the pome fruit, nut, or seed and produce aflatoxins — a group of carcinogenic fungal metabolites. A combination of aflatoxin in foods and a hepatitis B-susceptible human population such as exists in many parts of Africa and Asia can lead to high levels of liver cancer and elevated mortality — a major public health and food safety concern. This is an example of how the use of effective pest control carries with it the added benefit of reducing the carcinogen load due to toxic natural products such as aflatoxins in the food supply — a topic of food safety[17].

3 GMO crops

Chemical control of pests is widely practiced, but more and more the use of crops and animals genetically improved to resist pests (insects, disease, nematodes, weeds) are being explored and developed to offset chemical usage while protecting valuable food sources, in wheat, rice, and with many other crop staples and in food animals. In some cases, the resistance genes are engineered into the crop, giving farmers new genetic resources for insect resistance (e.g., *Bt* toxin genes in corn and soybeans). In these improved varieties, little or no external chemical insecticide application may be needed. Other crops (papaya and plums) have been made resistant to viral diseases by transgenically imparting production of viral coat proteins that stop virus reproduction[18].

Gene-based technologies, such as RNA interference (RNAi), are underpinning new technologies in pest control[19,20]. RNA interference is a natural process that affects the activity of genes. Research has successfully led to artificial RNAs that target genes in pest insects, slowing growth or killing them. The development of GMO crops that make RNAi harmful to their pests is under active exploration. As with most new technologies, there are safety concerns that RNAi might also harm desirable species.

Plant scientists are using CRISPR gene editing[21] to make sustainable agriculture crops with higher precision than possible before and less potential for undesirable side effects. The first examples will be in corn, planned for release for commercial plantings in about 2020. While these new technologies like gene editing will have a huge impact in agriculture and in design of new drugs, it is not clear whether they will be embraced by consumers, at least in the case of food products. Some environmental organizations have indicated that they will resist introduction of new crops and farm animals improved by gene modification. Even though new GMO technologies offer the promise of safer and more abundant foods, many consumers and activists are also interested in preserving the natural qualities of foods, including taste, texture, color and growth related characteristics that influence availability and market choice.

Seemingly, for every technological advance in developing resistance, the target pest evolves a strategy for overcoming the protection, as happened so often with resistance in insect and fungal pests previously controlled with synthetic pesticides and with antibiotic use in farm animals. This is possible with genetically modified crops and biopesticides, so requiring close monitoring of fields for early signs of resistance, and then applying an alternative pest control strategy from a "tool box approach" which may include conventional chemical pesticides, biopesticides, cultural methods, and other approaches is desirable to preserve these new technologies.

4 Smart application systems

Only small fraction of applied pesticides reach the intended pests, but rather bypasses the target and enters the soil, non-target vegetation, or are carried away by wind[22]. Agricultural engineers and systems scientists have developed more effective spraying techniques using spray drift control technology, electrostatically charged spray droplets, controlled release technology, or smart systems that direct spray just to the optimal position for contacting the target. These improvements save on the amount of pesticide needed for a particular situation, and also prevent inadvertent residues that can harm unintended crops, water way quality, or livestock and wild animals. But, they can also lead to more effective control of the target pest. Related to this, information is more accessible that clearly delineates the mere presence of a pest from the presence of a pest population of sufficient magnitude that can cause economic damage or impair safety in the harvested commodity. Not spraying at all can sometimes be the best strategy, generating a cycle of pest control by beneficial natural enemies, a means of biocontrol that, once fostered, can lead to sustainable pest suppression for many years[23,24]. This can have important ramifications in safety of foods, as lower chemical use may lead to safer foods as well as foods that are more widely available at relatively low costs.

Recent discussions with farming groups and food producers in China's Weifang Food Valley area of Shandong Province illustrate local efforts to reduce the use of conventional pesticides and fertilizers, including:

- Develop farming practices for organic produce and meat;
- Encourage use of biopesticides and biofertilizers;
- Control nematodes by non-chemical means, such as soil solarization;
- Develop novel ways of reducing development of resistance to pesticides;
- Introduce non-chemical insect and disease controls by biological or cultural means;
- Explore Traditional Chinese Medicine (TCM) approach to new antibiotics for use in farm animals and pest control;
- Assist in adoption and registration of biopesticides using an IR-4 type regional or national system such as in use in the US[25];

5 Conclusions

The field of pest management, in agriculture, public health and home use, is undergoing change as sole reliance on synthetic chemicals gives way to a variety of approaches, some with little or no pesticide in the mix. Health concerns over exposures to pesticides among agricultural workers and consumers of residue-tainted food products, as well as wildlife and non-target species, have been partly responsible for this, as have demands by consumers, translated through the food supply chain to large commercial retail outlets, commodity organizations, and regulatory agencies, for pesticide free, organic, and "green" products. Still, the reality is that feeding a world population expected to top 9 billion by 2050 will require the use of chemical pesticides as a primary tool in combatting pests in the field and in stored products, as well as for public health, for years to come. It may in fact increase use of pesticides as emerging economies of China, India, Brazil, and other nations expand agricultural production. But, the options for pest control have expanded, also illustrated by biopesticides, and advances in the fields such as genetics, biotechnology, sustainability, and more targeted pesticide application technology. These factors may in the long run reduce the need for chemical pest management tools to a fraction of that used presently.

Other transformative research opportunities that will require mathematical and physical science research efforts to improve the sustainability of agriculture include[26]:

- Ensuring a sustainable water supply for agriculture;
- Closing the loop for nutrient life cycles;
- Crop protection as noted in this manuscript;
- Innovations to prevent waste of food and energy;
- Sensors for food security and safety;
- Maximizing biomass conversion to fuels, chemicals, food and biomaterials.

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