Bioorganic & Medicinal Chemistry 17 (2009) 4022–4034

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Natural products in crop protection

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ARTICLE INFO

Article history:
Received 31 October 2008
Revised 14 January 2009
Accepted 22 January 2009
Available online 27 January 2009

Keywords:
Natural pesticide
Sustainable agriculture
Natural herbicide
Natural fungicide
Natural insecticide
Essential oils
Biological control
Triketone
Corn gluten
Momilactone
Sorgoleone
Bialaphos
Spinosad
Avermectins
Milbemycins
Ryania
Sabadilla
Chitin
Harpin
Strobilurins

ABSTRACT

The tremendous increase in crop yields associated with the 'green' revolution has been possible in part by the discovery and utilization of chemicals for pest control. However, concerns over the potential impact of pesticides on human health and the environment has led to the introduction of new pesticide registration procedures, such as the Food Quality Protection Act in the United States. These new regulations have reduced the number of synthetic pesticides available in agriculture. Therefore, the current paradigm of relying almost exclusively on chemicals for pest control may need to be reconsidered. New pesticides, including natural product-based pesticides are being discovered and developed to replace the compounds lost due to the new registration requirements. This review covers the historical use of natural products in agricultural practices, the impact of natural products on the development of new pesticides, and the future prospects for natural products-based pest management.

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1. Introduction

The success of modern agricultural practices is due in part to discovery and adoption of chemicals for pest control. Indeed, the tremendous increase in crop yields associated with the 'green' revolution would not have been achieved without the contribution of these synthetic compounds. The abundance of high quality food in developed nations has all but eliminated concerns about access to food in these countries. However, concerns over the potential impact of pesticides on the environment has now become more pressing and more stringent pesticide registration procedures, such as the Food Quality Protection Act in the United States,[1] have been introduced. These new regulations have reduced the number of synthetic pesticides available in agriculture. Therefore, the current paradigm of relying almost exclusively on chemicals for pest control may need to be reconsidered.[2]

New pesticides, including natural product-based pesticides are being discovered and developed to replace the compounds lost due to the new registration requirements.[3] New pesticides are also needed to combat the evolution of resistance to pesticides.[3] This review covers the historical use of natural products in agricultural practices, the impact of natural products on the development of new pesticides, and the future prospects for natural products-based pest management. We separate products or compounds that might be used in organic agriculture from those used in conventional agriculture, but make the disclaimer that not every product that we mention in the organic agriculture sections may be legally used in every country for organic agriculture. The rules regarding what is accepted for organic agriculture vary between countries and even between states and do not always have a scientific rational for inclusion or exclusion.[4,5] In general, organic agriculture does not accept synthetic versions of natural compounds. Organic

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0968-0896/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.bmc.2009.01.046

farmers need to consult with their certification agency or program to be sure that any material they use is 'certified' or acceptable as organic. Also, we do not cover biocontrol products (living organisms) for pest management, many of which are used by organic farmers. For the most part, we do not mention natural products that are not currently used in agriculture for pest management. Many natural compounds have been discovered and patented for such use, but are not commercially available for numerous reasons.

1.1. Crop protection, a historical overview

The need for producing more food within a particular area arose as nomadic populations of hunter-gatherers settled to form more permanent communities. For thousands of years, agricultural practices relied heavily on crop rotation or mixed crop planting to optimize natural pest control (such as predation, parasitism, and competition). Therefore, the concept of 'natural pesticides' arose early in the development of agriculture. Indeed, the Lithica poem (c. 400 B.C.) states 'All the pests that out of earth arise, the earth itself the antidote supplies'.[6] Greek and Roman scholars such as Theophrastus (371–287 B.C.), Cato the Censor (234–149 B.C.), Varro (116–27 B.C.), Vergil (70–19 B.C.), Columella (4–70 A.D.) and Pliny the elder (23–79 A.D.) published treaties on agricultural practices to minimize the negative effects of pests on crops. Methods such as mulching and burning, as well as the use of oils for pest control were mentioned. Chinese literature (ca. 300 A.D.) describes an elaborate system of biological control of caterpillar infestations in citrus orchards. Colonies of the predatory ants (*Oecophylla smaragdina*) were introduced in citrus groves, and bridges made of bamboo allowed the ants to move between trees. A survey of the Shengnong Ben Tsao Jing era (25–220 A.D.) shows that 267 plant species were known to have pesticidal activity.[7] Finally, the use of beneficial insects to control other insect pests was mentioned by Linnaeus as early as 1752, and he won a prize in 1763 for an essay describing the biological control of caterpillars.

The European agricultural revolution that followed in the 19th century was accompanied by more extensive and international trade that resulted in the discovery of botanical insecticidal powders from *Chrysanthemum* flower heads and *Derris* root which contain pyrethrum and rotenone, respectively. The advent of extensive monoculture and intensive agricultural practices of the 20th century was accompanied by increases in yields. New cultivars were selected based on their higher yields, but many of these lines seem to have lower resistance to pests. This has resulted in greater pest pressure, which has mostly been addressed by the use of synthetic pesticides.

1.2. Structural diversity in nature

A recent report probing the structural diversity of organic chemistry by performing a scaffold analysis of all the compounds available in the CAS registry confirmed that most of the 24 million organic compounds in the database can be classified in as few as 143 basic structural groups.[8] This is due primarily to the fact that molecular scaffoldings used in organic chemistry are limited. On the other hand, a study on the complementarity between synthetic and natural pharmacophores highlighted that natural products generally have a high structural diversity, possessing more chiral centers, sp^3-hybridized carbons, and rings than synthetic compounds.[9] Few natural products contain halogens (Cl, F, and Br), but they tend to be rich in oxygen and nitrogen, and may contain sulfate or phosphate groups. This diversity may serve as useful novel scaffoldings in developing new classes of natural product-based pesticides.[10–12] Therefore, new cheminformatic and synthetic techniques have been developed to identify and design compounds with natural product-like properties.[13–15]

The complexity of the carbon skeleton of natural products is the result of a natural 'high-throughput' screen to select compounds with appropriate biologically activities. The term 'high-throughput' does not refer to the speed of the selection, but rather to the innumerable permutations of relatively complex structures that have been synthesized by a very large number of biochemical machines (organisms) over an extremely long time. Furthermore, since these products are almost exclusively derived from pathways associated with secondary metabolism, these compounds have a high likelihood to possess some biological activity against other organisms, often via novel mechanisms of action,[2,16,17] which is particularly important since new modes of action are so deeply needed as pests continue to evolve resistance to the compounds currently available.

An important benefit of natural product-based pesticides is their relatively short environmental half-lives, which is due to the fact that they do not possess 'unnatural' ring structures and contain relatively few halogen substituents. While these compounds are perceived to be environmentally benign, very little is known about the fate of natural products in the environment.[18]

2. Natural products for weed management

The management of weeds has been a major problem since the inception of agriculture. In fact, unmanaged weeds cause greater reduction in crop yields than the presence of any other agricultural pest. Manual labor in ancestral farming practice is expended mostly on hand weeding of fields. Not surprisingly, modern agriculture relies heavily on the use of synthetic herbicides for managing weeds. This has been possible because synthetic herbicides are highly effective (active ingredient application rates can be as low as a gram per hectare).[19] Many of these compounds have very good selectivity toward crops and are relatively inexpensive to manufacture. While their use has become increasingly controversial, most currently used herbicides have low impact on the environment and wildlife. Today, herbicides account for more than half of the volume of all agricultural pesticides applied in the developed world and the public has expressed concern about the potential health and environmental impact of these compounds. Partly due to this, organic agriculture has received a recent surge in popularity.

2.1. Organic agriculture

Organic agriculture does not allow synthetic pesticides, including herbicides.[20,21] Weed management under organic agriculture practices is very problematic. While most methods rely on soil cultivation, hand hoeing, biocontrol, organic mulches, and ironically plastic (synthetic) ground cover, and the use of some natural products is permitted (Table 1). As opposed to synthetic herbicides, the available natural herbicides have little to no selectivity and they must be applied in relatively large quantities. Furthermore, little scientific literature is available on the use and environmental impact of natural products in organic agriculture.

2.1.1. Corn gluten meal

Corn (*Zea mays*, L.) gluten meal is a byproduct of corn milling. It is commercialized as both a fertilizer and a pre-emergence herbicide on lawns and high-value crops.[22–24] The commercial products contain between 50% and 100% of corn gluten and are sold under a variety of trade names (Table 1). However, control of grasses and other weeds requires extremely high rates (e.g., 2 tons per hectare) and is often cost prohibitive. Corn gluten has no effect on existing weeds, but it has a broad-spectrum of activity on the germination and development of young emerging plants.[25,26] Hydrolysis of corn

Table 1
Examples of commercial products containing natural products used for weed management in organic agriculture

Products	Components
WeedBan™ Corn Weed Blocker™	Corn gluten meal
Bioscape Bioweed™	Corn gluten meal, soybean oil
Scythe™	Pelargonic acid (57%), related short chain fatty acids (3%), 30% paraffinic petroleum oil (30%)
Burnout™ Bioganic™ Poison Ivy Defoliant™	Clove oil (12–18%), sodium lauryl sulfate (8–10%), acetic acid, lecithin, citric acid (30%), mineral oil (80%)
Bioorganic™	Clove oil (5%), 2-phenethyl propionate (5%), sesame oil (4%) and sodium lauryl sulfate (0.5%)
AllDown™	Citric acid (5%), acetic acid, yucca extracts, garlic oil (0.2%)
Interceptor™	10% pine oil
Weed Zap™	Clove oil or cinnamon oil (30%), vinegar (70%)
Weed-A-Tak™ Repellex®	Citric acid (32%), clove oil (8%), cinnamon oil (8%), 2-phenetyl proprionate, lecithin. It may contain thyme oil, and wintergreen oil.
Moss & Algae Killer™ Naturell WK Herbicide™ DeMoss™ Mosskiller™	Potassium salts of fatty acids (40%)
Organic Weed & Grass Killer™	Citrus oil (70%)
GreenMatch O™ Nature's Avenger™	D-Limonene (70%), castor oil (1 to 4%), emulsifiers (18 to 23%)
GreenMatch EX™	Lemongrass oil (50%) and a mixture of water, corn oil, glycerol esters, potassium oleate and lecithin
Matran II™	Clove oil (46%), wintergreen oil, butyl lactate, lecithin
Eco-Exempt™ Eco-Smart™	2-Phenethyl proprionate (21.4%), clove oil (21.4%)

gluten by soil microbes releases several phytotoxic dipeptides[27,28] and a phytotoxic pentapeptide (Fig. 2.1).[29] The exact mode of action of these oligopeptides is not known but they affect cell wall formation, membrane integrity, and nuclear development.[28] Corn gluten may be considered a slow-release proherbicide since it must be hydrolyzed to release the active ingredients.

2.1.2. Acetic acid

Acetic acid [CAS 64-19-7] (Fig. 2.2) has been used as a weed control agent for several centuries. Diluted aqueous solutions of up to 20% acetic acid are now sold as horticultural vinegar, or in mixtures with other natural products, for non-selective weed management (see subsequent sections).

Acetic acid is a burn down, non-selective herbicide. Therefore, it is used for non-cropland areas, such as railway rights-of-way, golf courses, open space, driveways and industrial sites. Acetic acid solutions (10–20%) provide greater than 80% control of most small weeds.[30] However, the cost of applying acetic acid was more than ten times greater than the cost of using the more effective synthetic non-selective herbicide glyphosate (*N*-(phosphonomethyl)glycine) for roadside vegetation management.

As is common with burn down herbicides, acetic acid kills the aerial portions of plants, but does not control the underground parts, and plants typically reemerge from the root system after a few days or weeks. The typical concentration of acetic acid in most commercially available vinegars is 5%, and this concentration is reported to provide only variable control of small weeds. Oil adjuvants do not significantly increase the herbicidal activity of acetic acid. Although acetic acid is applied at relatively high concentrations, it does not have a long term negative influence on soil microorganisms.[31]

Acetic acid can also be used to control invasive aquatic weeds. It kills propagules of hydrilla (*Hydrilla verticillata*), sago pondweed (*Stuckenia pectinatus*), and smooth cordgrass (*Spartina alterniflora*)[32,33] Careful treatments of lake sediments with acetic acid may have utility as an alternative to foliarly applied herbicides such as imazapyr and glyphosate.[33]

2.1.3. Fatty acids

The herbicidal activity of fatty acids has been known for many years[34,35] and some fatty acid salts are now marketed as non-selective herbicidal soaps. These are composed of fatty acids of various aliphatic length mixed with vinegar or acetic acid (Section 2.1.2) and emulsifiers such as organosilicone, saponified, methylated, and ethylated seed oil activator adjuvants.

Herbicidal soaps act relatively rapidly and have no selectivity (broad-spectrum weed control). However, most weeds tend to recover because there is no residual activity after the initial burndown effect which takes place soon after application.[36] As such, these mixtures can be used as desiccants. Fatty acids with mid-range aliphatic tails such as caprylic (C8, octanoic acid) and pelargonic acid (C9) are the most effective.[37]

Pelargonic acid [CAS 112-05-0] (Fig. 2.2) is a contact, broad-spectrum commercial herbicide for control of annual weeds, mosses (*Bryum argenteum*) and liverwort (*Marcbantia polymorpha*).[19,38,39] It disrupts plant cell membranes, causing rapid loss of cellular function.[39] When saturated fatty acids from C6 to C14

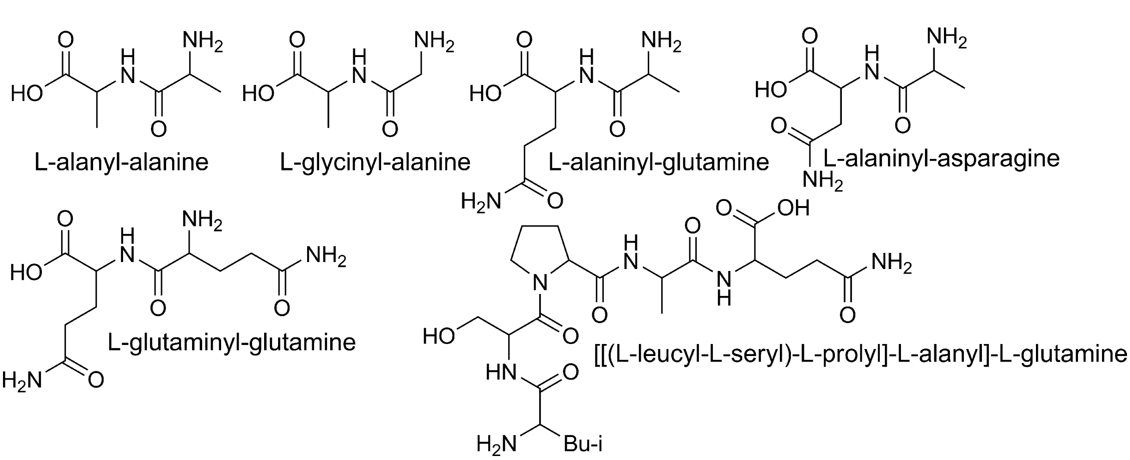

Figure 2.1. Structures of the phytotoxic oligopeptides in the hydrolisate of corn gluten meal used for weed management in organic agriculture.

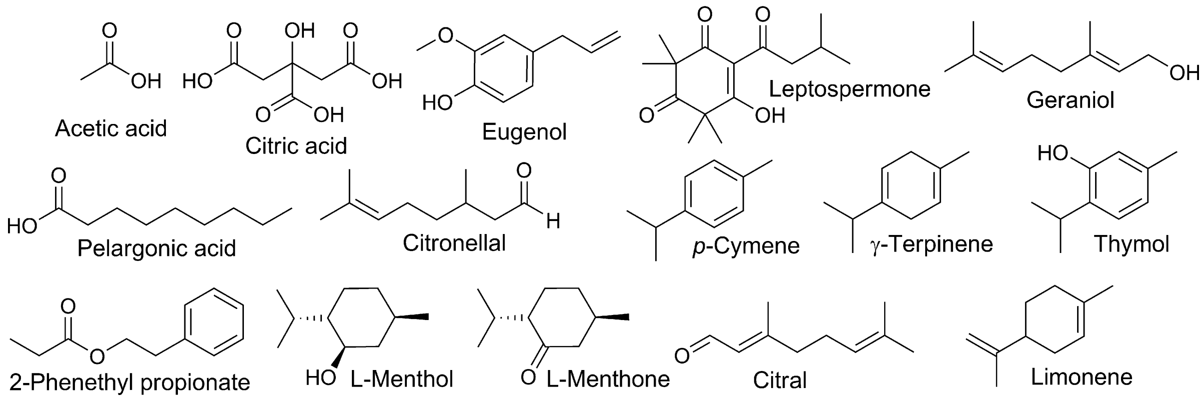

Figure 2.2. Structures of the natural herbicides or main component of mixtures used for weed management in organic agriculture.

were compared, the C9–C11 fatty acids were especially active, whereas the others were significantly less active.[40] C6 and C14 fatty acids had essentially no herbicidal activity. Pelargonic acid itself is considered a low toxicity and environmental impact herbicide.[19,34] It has no residual activity.

Adding organic acids such as succinic, lactic or glycolic acid enhance the efficacy of pelargonic acid formulations.[41] Potassium salts of fatty acid (up to 40%) preparations are commercialized, effective non-selective herbicides used for controlling mosses and liverworts (Table 1). Oleic acid is usually a major component of these mixtures, though the exact compositions of these products are not well publicized.

2.1.4. Essential oils

Essential oils have also shown some potential as herbicides. Surfactants, which are also limited in organic agriculture, are often required to assist in the spreading of the material. Since most essential oils commercialized for natural weed control consists of mixtures, it is difficult to cover the numerous formulations available. This section will highlight some of the most common oils used. All commercialized essential oils act as non-selective, contact herbicides (burn down) that can provide good but transient weed control.

The use of essential oils for weed control in organic agriculture seems promising, but these natural herbicides all act very rapidly and their efficacy is limited by the fact that they most likely volatilize relatively quickly. Alternative formulations, such as microencapsulation, are being developed to reduce the amounts applied, increase the duration of their effectiveness by reducing their volatilization, simplify the handling of material, and slow down the rate of degradation in the environment.[42]

2.1.4.1. Pine oil. Pine oil [CAS 8002-09-03] composed of terpene alcohols and saponified fatty acids is sold as a 10% aqueous emulsion for weed control (Table 1).[30] As with other natural product-derived weed control, pine oil did not provide the level of control obtained with a single application of glyphosate.[30]

2.1.4.2. Clove oil. The essential oil obtained by steam distillation of clove (*Eugenia caryophyllus* Spreng) leaves [CAS 8000-34-8] contains primarily eugenol [CAS 97-53-0] (Fig. 2.2) in together with several other terpenoids. Clove oil is commercialized for weed control under several forms (Table 1). For example, Matran® contains up to 50% clove oil and Burnout II® consists of a mixture of 12% clove oil with acetic acid. Clove oil has also been formulated for the control of poison ivy (*Rhus radicans* L.). Clove oil applied at concentrations of 1–5% controlled most small weeds,[43] but the relatively high rate required for control makes this treatment expensive, even in high-value vegetable production systems.

2.1.4.3. 2-Phenethyl propionate. 2-Phenethyl propionate [CAS 122-70-3] (Fig. 2.2) is a component of peppermint (*Mentha piperita*, L.) oil [CAS 8006-90-4], which is also rich in menthol [CAS 89-78-1] and menthone [CAS 89-80-5] (Fig. 2.2).[44] 2-Phenethyl propionate has been patented as a herbicide[45] and can be found as a component of the formulations of natural herbicides (Table 1). This product must be diluted before application and its use recommendations are similar to those of clove oil or eugenol (see above Section 2.1.4.2). This compound is thought to be very safe to the environment and to human health, as it is used in food flavorings.

2.1.4.4. Lemongrass oil. Lemongrass (*Cymbopogon citratus* Stapf. or C. *flexuosus* D.C.) oil [CAS 8007-02-1] (Table 1) has recently been commercialized as an organic herbicide, but its potential use for weed control was first patented in England in 1924.[46] The main component (80%) of this oil is citral [CAS 5392-40-5](Fig. 2.2).[47] A commercial product containing 50% lemongrass oil must be diluted to 7–15% before application. Lemongrass oil acts as a contact herbicide, and since the active ingredient (citral) does not translocate, only the portions of plants receiving the spray solution are affected.

Application of lemongrass oil apparently provides weed control that is superior to that obtained with application of products containing technical grade D-limonene [CAS 5989-27-5] (Fig. 2.2) alone. D-Limonene is known to remove the waxy cuticular layer from the leaves of the plants treated, causing rapid dehydration and death of the tissues.

2.1.4.5. Citronella oil. Citronella oil [CAS 8000-29-1], which is best known for its use as a mosquito repellent, has been tested as a herbicide in tree nurseries.[48] This oil is obtained from several sources, but *Cymbopogon* spp. are the most common. The primary components are citronellal (42%), geraniol (21%) and other terpenes (Fig. 2.2). Tests done in tree nurseries showed that citronella oil provided some weed control while not causing adverse effects on dormant broadleaf trees; however, conifer species were very sensitive to this treatment.

2.1.4.6. Other essential oils. Many other plant essential oils show potential as natural herbicides, but these remain to be commercialized. Eucalyptus oil extracted from *Eucalyptus citriodora* has been tested as a potential natural herbicide. This phytotoxic oil consists primarily of citronellal (77%) (Fig. 2.2) and other small terpenes.[49] In particular, eucalyptus proved to be effective as an alternative control of little seed canarygrass (*Phalaris minor* Retz.).[50]

Natural oils from neem (*Azadirachta indica* Juss.) [CAS 8002-65-1], coconut (*Cocos nucifera* L.) [CAS 8001-31-8], and sunflower (*Helianthus annuus* L.) [CAS 8001-21-6] controlled the parasitic weed within 2–3 days of application. Castor (*Ricinus communis* L.)

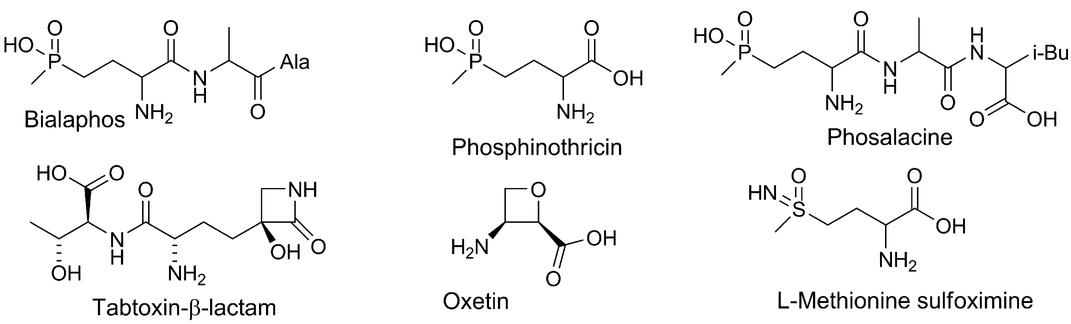

Figure 2.3. Structures of natural herbicides used in conventional agriculture and related compounds.

[CAS 8001-79-4] and niger (*Guizotia abyssinica* (L. fil.) Cass.) oils killed the weed within 3–4 days, and mustard (*Brassica juncea* (L.) Czernjaew) oil required 5 days to kill the bud.[51]

Essential oils of various varieties of oregano (*Origanum* spp.) and basil (*Ocimum basilicum*) have been tested against barnyardgrass (*Echinochloa crus-galli* (L.) P. Beauv.) and common lambsquarter (*Chenopodium album* L.) with some success.[52] These oils, which are composed primarily of *p*-cymene (20–25%), γ-terpinene (15–20%), thymol (10–35%), have been patented for moss control (Fig. 2.2).[53]

Manuka oil is isolated from the leaves of *Leptospermum scoparium*. It is composed of sesquiterpenes (up to 70%)[54] and is rich in β-triketones.[55,56] Leptospermone [CAS # 567-75-9] (Fig. 2.2), the most abundant triketone of these oils, causes bleaching of the foliage of grasses and broadleaf plants.[57,58] These natural triketones are structurally similar to some synthetic herbicides (e.g., sulcotrione and mesotrione) and have the same molecular target site, namely *p*-hydroxyphenylpyruvate dioxygenase (HPPD).[59,60]

2.1.5. Prospects of natural products used in organic agriculture

The use of organic weed management tools may be enhanced in the context of an integrated pest management program that include sowing multiple crops, extended rotation cycles, mulching, and soil cultivation and cover. However, as opposed to traditional synthetic herbicides, none of the natural herbicidal compounds allowed for use in organic agriculture are very active; therefore, they must be applied in relatively large quantities. This may lead to undesirable effects on the environment and the soil fauna and microbes, which is in direct opposition with the philosophical positions and purpose of those who practice organic agriculture. As well, these weed management tools have very little crop selectivity and still require laborious application methods to ensure they do not come in contact with the desired crop. Finally, organic weed management methods may be possible in small scale farming and high-value crops but do not seem feasible in the production of the agronomic crops such as grains grown on large-scale farming enterprises.

2.2. Conventional cropping systems

Discovery programs by the agrochemical industry are mostly driven by large-scale synthetic programs followed by screening to identify potential new herbicides. Most companies have a more modest effort to evaluate natural products from outside sources and, to a lesser extent, from in-house isolation efforts. While the literature is replete with reports of the isolation and characterization of phytotoxins from many sources, and many of these compounds have been patented for potential use as herbicides,[61] the use of natural or natural product-derived herbicides in conventional agriculture is limited.

2.2.1. Bialaphos

Bialaphos [CAS 35597-43-4] (Fig. 2.3), a tripeptide obtained from the fermentation culture of the actinomycete *Streptomyces hygroscopis*, is the only true commercialized natural product herbicide. It is a proherbicide that is metabolized into the active ingredient L-phosphinothricin [3559-44-5] (Fig. 2.3) in the treated plant.[62] Phosphinothricin is also produced synthetically as a racemic mixture of L- and D-phosphinothricin for commercialization as glufosinate [51276-97-2] (Basta®, Liberty®).

Bialaphos and phosphinothricin inhibit glutamine synthetase. Inhibition of glutamine synthetase, which is necessary for the production of glutamine and for ammonia detoxification, is lethal to plants. Plants exposed to glufosinate have reduced glutamine and increased ammonia levels in their tissues, which stops photosynthesis and results in plant death.[19,63]

Phosphinothricin is translocated symplastically and apoplastically throughout treated plants and it is not susceptible to metabolic degradation. While these are the only products available to have this mode of action, other natural products such as tabtoxine-β-lactam (CAS 40957-90-2), oxetin (CAS 94818-85-6), phosalacin (CAS 92567-89-0) and methionine sulfoximine (CAS 15985-39-4) (Fig. 2.3) also target this enzyme.[62]

Both bialaphos and phosphinothricin are broad-spectrum post-emergence herbicides that can be used for total vegetation control in many agricultural settings, or in non-cultivated areas and to desiccate crops before harvest. Because glufosinate is a broad-spectrum herbicide (little to no selectivity), it is often marketed along with genetically engineered glufosinate-resistant crops (soybean, corn and cotton).[63] These plants were transformed with a microbial *pat* transgene (phosphinothricin acetyl transferase) that detoxifies the inhibitor. While transgenic crops are not accepted in some parts of the world, the technology has been widely accepted in the western hemisphere.

2.3. Allelopathy

Theophrastus (371–287 B.C.) wrote about the inhibitory effect of pigweed on alfalfa. As early as 1832, the Swiss botanist De Candolle suggested that 'soil sickness' associated with plants grown in some rotations was due to exudates of crops. The deleterious effect of black walnut trees on the growth of plants in the surrounding was reported fifty years later.[64] It took another fifty years to coin the term allelopathy, which was constructed from the two Greek words *allelo* and *pathy*, to mean mutual harm.[65] This definition was later expanded by Rice to include both inhibitory and stimulatory effects of one plant (or microorganism) upon another via a chemical (allelochemical).[66] While allelopathy does not involve the direct application of natural products for weed management, and other factors such as competition for resources undoubtedly contribute to the overall control of weeds, this small section highlights instances where specific allelochemicals were identified as being the primary

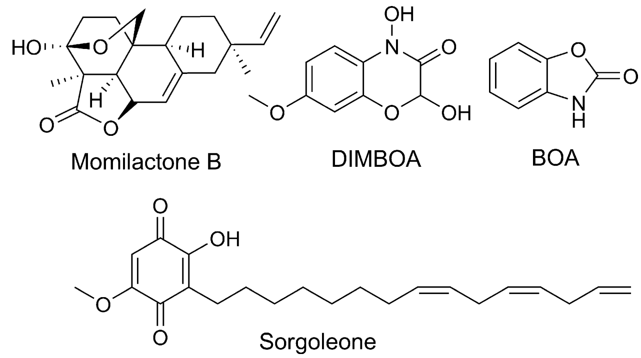

Figure 2.4. Structures of natural products involved in allelopathic interactions.

molecules involved in weed control by crops. Those interested in this topic are encouraged to read recent reviews.[67,68]

2.3.1. Momilactone B

A significant effort to generate highly allelopathic rice varieties is underway.[69,70] Thousands of varieties have been screened for allelopathic potential, and up to 4% of varieties can suppress important paddy field weeds. While the level of weed management obtained to date is not equivalent to that obtained with herbicides, herbicide use rates can be substantially reduced in paddy fields planted with allelopathic varieties.[71]

Momilactone B [CAS 51415-08-8] plays a key role in rice (*Oryza* spp.) allelopathy[72] (Fig. 2.4). Some rice varieties release up to 2–3 µg of momilactone/plant/day,[73] which is sufficient to inhibit the germination and growth of neighboring weeds.[74] Nothing is known about the mode of action of momilactone B.

2.3.2. Sorgoleone

Sorgoleone [CAS 105018-76-6], a lipid benzoquinone that exudes from the roots of sorghum (*Sorghum bicolor* L.) (Fig. 2.4),[75–78] suppresses the growth of a large number of plant species, but it is most active on small-seeded plants.[77,79–83] Sorghum accumulates sorgoleone and its analogues in mature root hairs,[84,85] and the production (approximately 18 mg g^{-1} root dry weight) is optimum at temperatures ranging from 25 to 35 °C.[84]

The in vivo mechanism of action of sorgoleone and its analogs is unclear, but it is known to inhibit several physiological processes and enzymes in plants (e.g., photosynthetic and mitochondrial electron transport,[77,78,86,87] *p*-hydroxyphenylpyruvate dioxygenase,[88] and root H+-ATPase and water uptake[89]). Sorgoleone applied to soil is easily recovered within 1 h of application (85%). The recovery rate decreases over time, though low levels of sorgoleone are still extractable after 6 weeks. Sorgoleone degrades slowly to yet uncharacterized metabolites, but more research needs to be done to better characterize the fate of sorgoleone in soil.[90]

2.3.3. Benzoxazinoids

Allelopathic benzoxazinoids isolated in significant amount from many species within the Poaceae family have potential uses in agriculture as weed control agents.[91] Benzoxazinoids such as 2(3*H*)-benzoxazolone (BOA) [CAS 59-49-4] and 2,4-dihydroxy-7-methoxy-(2*H*)-1,4-benzoxazin-3(4*H*)-one (DIMBOA) [CAS 15893-52-4] (Fig. 2.4) exist mostly as glucosides within the producing plants.[92] However, these glucosides are subject to microbial degradation when released into the environment, which release the aglycone moieties. These unstable aglycones undergo further degradation (hydrolysis and ring contraction) into the corresponding benzoxazolinones with short half-lifes (1 day for DIMBOA).[93,94] Benzoxazolinones might be further transformed, either chemically or by soil microbes, into more toxic degradation products.[93]

3. Natural products for insect management

One of the more noticeable trends in pesticide sales over the past 25 years is the increasing market share of herbicides relative to other pesticides. In 2004, herbicides accounted for 45.4% of the agrochemical market, followed by insecticides 27.5%, fungicides 21.7% and other products 5.4%.[95]

Recent reports indicate that the use of natural product and natural product-derived insecticides continue to increase, whereas sales of organophosphates are declining. Indeed, three out of the five most commonly used insecticides classes (neonicotinoids, pyrethroids, and other natural products) are natural product or natural product-derived, accounting for 19.5%, 15.7%, and 7.6% of the combined worldwide sales.[96]

3.1. Neem-based products

The seeds from the Indian neem tree, *A. indica* (A. Juss.), are the source of two types of neem-derived botanical insecticides; neem oil and medium polarity extracts. Neem seeds contain numerous azadirachtin analogs (Fig. 3.1), but the major form is the tetranortriterpenoid, azadirachtin or azadirachtin A, and the remaining minor analogs likely contribute little to the overall efficacy of the extracts.[97] According to the CRC Press Dictionary of Natural Products at least 237 different compounds have been isolated from the genus *Azadirachta*[98] with the majority of these from the species *indica*, which attests to the importance and large interest in this plant. Typically solvent partitions or other chemical processes are required to concentrate this active ingredient to the level of 10–50% seen in the technical grade material used to produce some commercial products.[97]

Azadirachtin is well known as a potent antifeedant to many 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.[97] Many neem/azadirachtin-based products are approved for use as organic insecticides and marketed under such names as Ecozin, Azatrol EC, and Agroneem. Azadiractin-based products are recommended in the control of insects such as aphids, armyworms and other caterpillars, beetles (including Colorado potato beetle), borers, budworms, cutworms, leafhoppers, leafminers, lepidopterous larvae, loopers, lygus, maggots, mealy bugs, psyllids, scale, stink bugs, weevils, whiteflies, and other insects.

3.2. Spinosads

Spinosad (Fig. 3.2) is a mixture of spinosyn A and spinosyn D, originally isolated from the soil Actinomycete, *Saccharopolyspora spinosa*. Spinosad is recommended for the control of a very wide range of caterpillars, leaf miners, thrips and foliage-feeding beetles. Spinosad is sold as concentrated aqueous formulations under several trade names.[3,99]

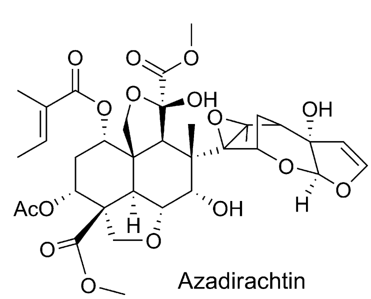

Figure 3.1. Structure of the major bioactive constituent in Neem.

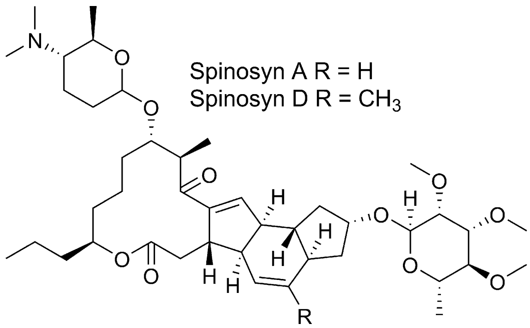

Figure 3.2. Structure of the major bioactive constituents isolated from the soil actinomycete, *Saccharopolyspora spinosa*.

Spinosyns have a novel mode of action, primarily targeting binding sites on nicotinic acetylcholine receptors that are distinct from those at which other insecticides exert their activity, leading to disruption of acetylcholine neurotransmission.[100,101] Spinosad also has secondary effects on γ-amino-butyric acid neurotransmission. The result of this mode of action is hyperexcitation and disruption of an insect's nervous system.[100] Spinosad is approved for use as an organic insecticide under the name Entrust™ (Dow AgroSciences/Mycogen), among others. Spinosad is recommended for the control of a very wide range of caterpillars, leaf miners, thrips and foliage-feeding beetles. Spinosad may also be used on row crops (including cotton), vegetables, fruit trees, turf, vines and ornamentals.[3,102,103]

3.3. Pyrethrum

Pyrethrum refers to the oleoresin extracted from the dried flowers of *Tanacetum cinerariaefolium* (Asteraceae) and is the source of the pyrethrins, chrysanthemates and pyrethrates.[3,97] Among the natural pyrethrins, those incorporating the alcohol pyrethrolone, namely pyrethrins I and II (Fig. 3.3), are the most abundant and account for most of the insecticidal activity.[97] It is worth clarifying that pyrethrins as pyrethrum will be discussed in this section; however, synthetic pyrethrins will not be discussed since the topic could fill a review article alone.

The symptoms of pyrethrin poisoning are characterized by hyperexcitation, convulsions, seizures, and finally followed by death.[104,105] These symptoms are a result of the neurotoxic action, which block voltage-gated sodium channels in nerve axons. Unfortunately, the pyrethrins are extremely unstable when exposed to air and ultraviolet light; however, they are recommended for control of a wide range of insects and mites on fruit, vegetables, field crops, ornamentals, glasshouse crops and house plants, as well as in public health, stored products, animal houses and on domestic and farm animals. Pyrethrum is approved for use as a broad-spectrum organic insecticide under many trade names (e.g., Pyganic and Diatect 5).

3.4. Rotenone insecticides

Rotenone has been used as an insecticide for over a century and its use as a fish poison dates back even further.[97,106] Typically,

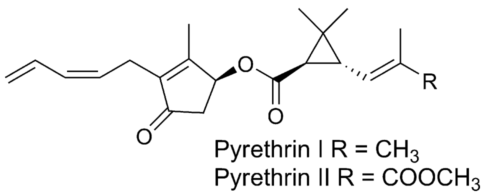

Figure 3.3. Structure of the major constituents of pyrethrum.

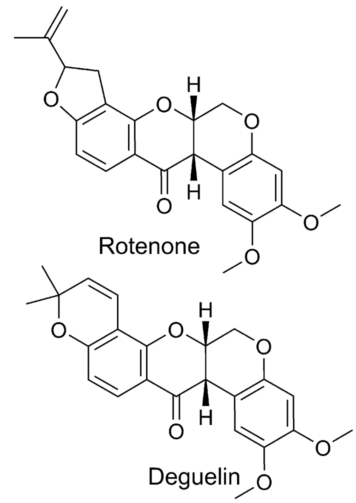

Figure 3.4. Structures of rotenone and deguelin; major constituents in rotenone insecticides.

products containing rotenone are preparations from plant of the genus *Derris* or *Lonchocarpus* (Leguminosae). The principal commercial form of the botanical insecticide rotenone comes from Cubè resin, a root extract of *Lonchocarpus utilis* and *Lonchocarpus urucu*. Although rotenone is the primary major constituent in products containing these preparations, a second isoflavone, deguelin, also contributes significantly to the activity (Fig. 3.4).[107–109] Rotenone blocks respiration by inhibition of electron transport at the complex I,[110,111] and products containing rotenone are commercialized as broad-spectrum insecticides under many trade names (e.g., Bonide Rotenone 5).

3.5. Avermectins and milbemycins

The structurally similar avermectins and milbemycins, both discovered from *Streptomyces* sp. culture broths, have had huge impacts in the field of animal health as agents against worms, ticks and flies.[112,113] The impact as crop protection insecticides has been less dramatic but nevertheless significant. Abamectin, a natural fermentation product of *Streptomyces avermitilis* contains > 80% avermectin B_{1a} and <20% avermectin B_{1b} (Fig. 3.5).[114]

The avermectins are both insecticides and acaricides which are effective by either contact or ingestion. The target for avermectins is the GABA receptor in the peripheral nervous system.[115] Avermectins stimulate the release of GABA from nerve endings and enhance the binding of GABA on the post-junction membrane of muscle cells of insects and other arthropods. This eventually results in an increased flow of chloride ions into the cell, with consequent hyperpolarisation and elimination of signal transduction, resulting in an inhibition of neurotransmission.[116] Avermectins are not registered as organic insecticides.

Milbemectin is derived from the soil bacterium *Streptomyces hygroscopicus* subsp. *Aureolacrimosus*, and used for mites and some insects control.[117] The predominant milbemectin component of commercial products is a mixture of milbemycins containing ⩾70% milbemcin A_4 and ⩽30% milbemycin A_3. Fig. 3.5.[118] Milbemycin has the same mode of action as that of avermectins in that they potentiate glutamate and GABA gated chloride-channel opening.[119] No organic insecticides containing milbemycins have been commercialized.

3.6. *Ryania speciosa* preparations

Having been in use for more than half a century, *Ryania* is an insecticide obtained from the roots and stems of a South American

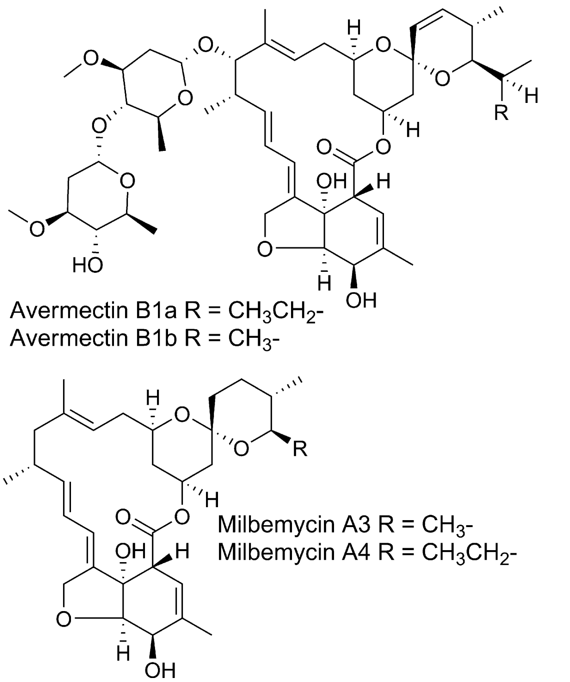

Figure 3.5. Structures of avermectins and milbemycins.

shrub (*R. speciosa*).[120] *Ryania* consists of powdered parts of *R. speciosa* that contains up 0.16–0.2% of the bioactive ryanodine (Fig. 3.6), a complex polycyclic, polyhydroxylic diterpene.[121]

Ryanodine is effective by either contact or ingestion. Ryanodine and related alkaloids affect muscles by binding to the calcium channels in the sarcoplasmic reticulum. This causes calcium ion flow into the cells, and death follows very rapidly.[122,123] *Ryania* controls codling moth caterpillars, leaf eating beetles and thrips and is frequently used in the organic orchard industry. It has relatively low toxicity to mammals. *Ryania* preparations are available commercially as organic insecticides by at least one manufacturer (Progressive Agri-Systems).

3.7. Sabadilla

Sabadilla is derived from the seeds of plants from the genus *Schoenocaulon* and is predominantly from the sabadilla lily (*Schoenocaulon officinale*). Sabadilla has been used as an insecticide for many years by native people of South and Central America. The activity of sabadilla preparations has been attributed to the alkaloids cevadine and veratridine which typically exist in a 2:1 ratio and are collectively referred to as veratrine (Fig. 3.7).[124] Veratrine alkaloids from sabadilla have a mode of action that is similar to that of the pyrethrins. They are non-systemic insecticides with contact action. Initial effects include paralysis, with death occurring later.[3,125,126] Sabadilla has been used commercially since the 1970s, and is approved for use as an organic insecticide under the trade names 'Red Devil' or 'Natural Guard' for use on many vegetables. Sabadilla is considered among the least toxic of botanical insecticides, with an oral LD_{50} of 4000–5000 mg/kg. Sabadilla is effective by either contact or ingestion and has been effective against caterpillars, leaf hoppers, thrips, stink bugs and squash bugs.

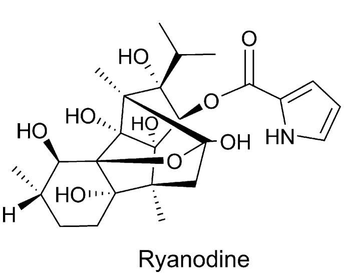

Figure 3.6. Structure of *Ryania* constituent.

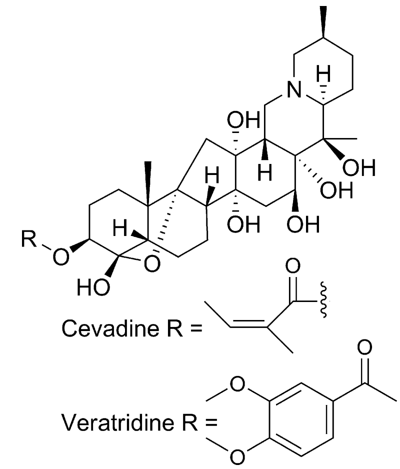

Figure 3.7. Structure of Sabadilla bioactive alkaloids.

3.8. Nicotine

Aqueous tobacco (*Nicotiana tabacum, N. glauca or N. rustica*) extracts containing the alkaloid nicotine (Fig. 3.8) have long been used to control crop insect pests.[127] Nicotine exerts its insecticidal effect by mimicking acetylcholine and interacting with nicotinic acetylcholine receptors (nAChRs), a major excitatory neurotransmitter in the insect CNS.[128] After acetylcholine is released by the presynaptic cell, it binds to the postsynaptic nicotinic acetylcholine receptor and activates an intrinsic cation channel.[129,130] The insecticide usually is marketed as a 40% liquid concentrate of nicotine sulfate, which is diluted in water and applied as a spray. Nicotine is used primarily for piercing-sucking insects such as aphids, whiteflies, leafhoppers and thrips.[131] Unfortunately, nicotine is highly toxic to mammals and extreme care must be used since it is readily absorbed through the skin. Organic nicotine products are available and approved for use under several names (e.g., Tobacco Dust).

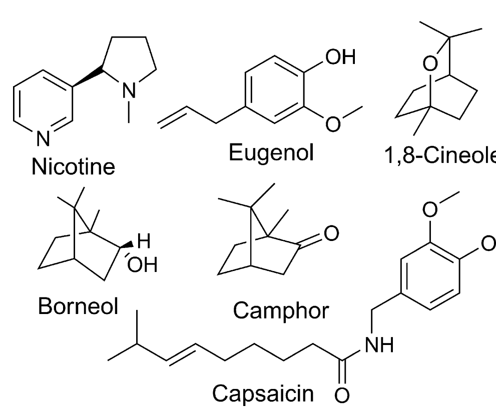

Figure 3.8. Constituents of nicotine products, rosemary oil, thyme oil, capsaicin preparations, and clove oil.

3.9. Essential oils and miscellaneous natural product preparations

Plant essential oils and seed pressed oils make up a significant part of the market share for natural product-based insecticides according to the Organic Materials Review Institute (OMRI).[132] Unfortunately, it is not within the scope of this review to discuss every essential oil currently being utilized for crop protection nor is it possible to discuss the barrage of various oil combinations. However, rosemary oil, thyme oil, and eugenol and/or clove oil are commonly used and are briefly discussed below. Many of these oil-based products also possess herbicidal activity (see Section 2.1.4).

3.9.1. Rosemary oil

Rosemary oil is obtained by steam distillation of the fresh flowering tops of both the wild-growing and cultivated shrub *Rosmarinus officinalis*, which is a species native to the Mediterranean region.[133] As with most essential oils, they are mixtures of numerous volatile organic compounds including primarily terpenoids and small aromatics. Rosemary oil consists primarily of 25% 1,8-cineole, borneol, camphor and high amounts of monoterpenoids (Fig. 3.8). Many of these constituents possess insecticidal activity.[134] Rosemary products are recommended for the control of aphids, beetles, whiteflies, spider mites, thrips, and caterpillar larvae, among other. Products available commercially include multiple products from EcoSMART Technologies one of which is a mixture of 10% rosemary oil and 2% peppermint oil called Ecotrol® EC Insecticide/Miticide. Rosemary oil is exempt from EPA registration and is therefore available for use in organic farming.

3.9.2. Thyme oil

Thyme oil is obtained by steam distillation of fresh or partially dried aerial parts of flowering wild or cultivated *Thymus vulgaris* or other species from the same genera. It is also native to the Mediterranean region and cultivated in regions mentioned above for rosemary. The oil consists of thymol and carvacrol as the main constituents together with numerous additional monoterpenoids.[133] Thyme oil products are exempt from EPA registration and are therefore available for broad-spectrum insect control in organic farming. Commercial products containing thyme oil include Proud 3 from BioHumaNetics, Inc., Organic Yard Insect Killer from Green Light, among others.

3.9.3. Clove oil

Clove oil is obtained via water distillation from dried flower buds of the tropical tree *Syzygium aromaticum* (syn. *Eugenia caryophyllata*), and it is not uncommon for the stems and leaves to also be utilized. Clove oil is usually over 92% eugenol and also contains eugenyl acetate and β-caryophyllene.[133] Eugenol is a fast acting contact insecticide that is effective on a wide variety of household arthropod pests and is also used on some ornamental plant pests such as armyworms, thrips, aphids and mites. Commercial products containing clove oil include Organic Yard Insect Killer from Green Light and Biooganic Lawn and Garden Spray from Bioganic Brand.

3.9.4. Capsaicin oil and preparations

Capsaicin-based products are obtained from the genus *Capsicum* and are often derived from hot chili peppers (*Capsicum frutescens*, Mill.). Resin products containing approximately 3% capsaicin are obtained by grinding dry, ripe peppers and extracting the powder. It is unclear whether the insect pest control effects of capsaicin products are due to its insecticidal effects or it repellency, as both are likely to contribute. Products containing capsaicin include Hot Pepper Wax Insect Repellent from Hot Pepper Wax, Inc. and Hot Pepper Wax from Bonide.

4. Natural products for plant pathogen management

Natural products for plant pathogen management have been the topic of or included in several previous reviews.[135–137] Many natural compounds and preparations have been described with activity against bacterial or fungal plant pathogens. Indeed, plants protect themselves from microbial attacks with both constitutive antimicrobials and compounds induced by the attacking pathogen (phytoalexins). Phytoalexins have not been directly exploited as fungicides, but natural products have been used to indirectly protect plants from pathogens by induction of systemic acquired resistance (SAR), including phytoalexins. These SAR-inducing compounds and preparations are termed elicitors. Since such activity is indirect, the pathogen cannot evolve resistance directly to the elicitor, making such products excellent candidates for integrated disease management. Elicitors are generally not as effective as good chemical fungicides partly because the timing of elicitor application and threat to the crop by a pathogen is crucial, but difficult to maximize.

4.1. Organic agriculture

A range of microbially-derived products are available for management of plant diseases in organic agriculture. However, several purely natural fungicides (e.g., blastocidin-S) are used only in conventional cropping systems.

4.1.1. Plant essential oils

Several plant essential oils are marketed as fungicides for organic farmers. These include jojoba (*Simmondsia californica*) oil (e.g., E-Rase™), rosemary (*Rosemarinus officianalis*) oil (Sporan™), thyme (*T. vulgaris*) oil (Promax™), clarified hydrophobic extract of neem (*A. indica*) oil (Trilogy™), and cottonseed (*Gossypium hirsutum*) oil with garlic (*Allium* sativum) extract (31% and 23%, respectively in GC-3™). Few scientific papers deal with these products and the actual active components, and their modes of action against individual plant pathogens are largely unknown.

4.1.2. Extract of giant knotweed

An extract of the giant knotweed (*Reynourtria sachalinensis*) (Milsana™) is used in Europe for the control of a wide spectrum of both fungal and bacterial plant diseases in both organic and non-organic agriculture. It is especially effective against powdery mildews and is used primarily on glasshouse and ornamental plants. It is sold as Regalia™ by Marrone Organic Innovations in the US for both food and non-food plants, but the current formulation is not yet accepted for organic agriculture. It apparently acts indirectly by induction of plant defenses.[138,139] Down-regulating chalcone synthase, a key enzyme of the flavonoid pathway, resulted in the nearly complete suppression of induced resistance by this product.[140] The main active elicitor compound(s) of this preparation are physcion and emodin,[141] a known antimicrobial compound.[142] While most of the activity seems to be associated with physcion, the photodynamic compound emodin can also generate reactive oxygen species in the presence of sunlight[143] Therefore, emodin-dependent oxidative stress may also induce SAR to plant pathogens.[144]

4.2. Conventional cropping system

4.2.1. Antibiotics from actinomycetes

A relatively large number of fermentation secondary products from actinomycetes, mostly *Streptomyces* spp., are fungicidal. Some of them have been commercialized and used extensively as agricultural fungicides in Japan, and to a lesser extent in other parts of the world. Since these compounds are considered antibiotics, they are not accepted for organic farming in the U.S.-except for streptomycin for fire blight control in apples and pears (http://www.omri.org/pages2-3.pdf). This is paradoxical since streptomycin is an important pharmaceutical and, to our knowledge, none of the others mentioned below are used as human pharmaceuticals.

Blasticidin-S (Fig. 4.1) (Bla-S™) from the soil actinomycete, *Streptomyces griseochromogenes* is used as a curative treatment against rice blast disease in eastern Asia.[145] It inhibits protein synthesis in target pathogens. Some blasticidin-S-resistant microbes detoxify the fungicide by deamination. It is active on a wide range of pathogens, but can cause damage to some crops.

Kasugamycin (Fig. 4.1) (Kasugamin™, etc.) from *Streptomyces kasugaensis* has been used for rice blast and other crop diseases in Japan. It interferes with tRNA/ribosome interactions and inhibits protein synthesis.[146] Mildiomycin (Fig. 4.1) (Mildiomycin™) from the soil actinomycete *Streptoverticillium rimofaciens* is used primarily in Japan for control of powdery mildews. Its mode of action is thought to be inhibition of protein synthesis by targeting peptidyl-transferase.[147] Natamycin (Fig. 4.1) (Delvolan™) from *Streptomyces chattanoogensis* is used primarily on ornamentals. It has a novel mode of action by binding ergosterol, an integral component of fungal cell membranes, thereby causing membrane dysfunction.[148] *Streptomyces rimosus* produces oxytetracycline (Fig. 4.1)

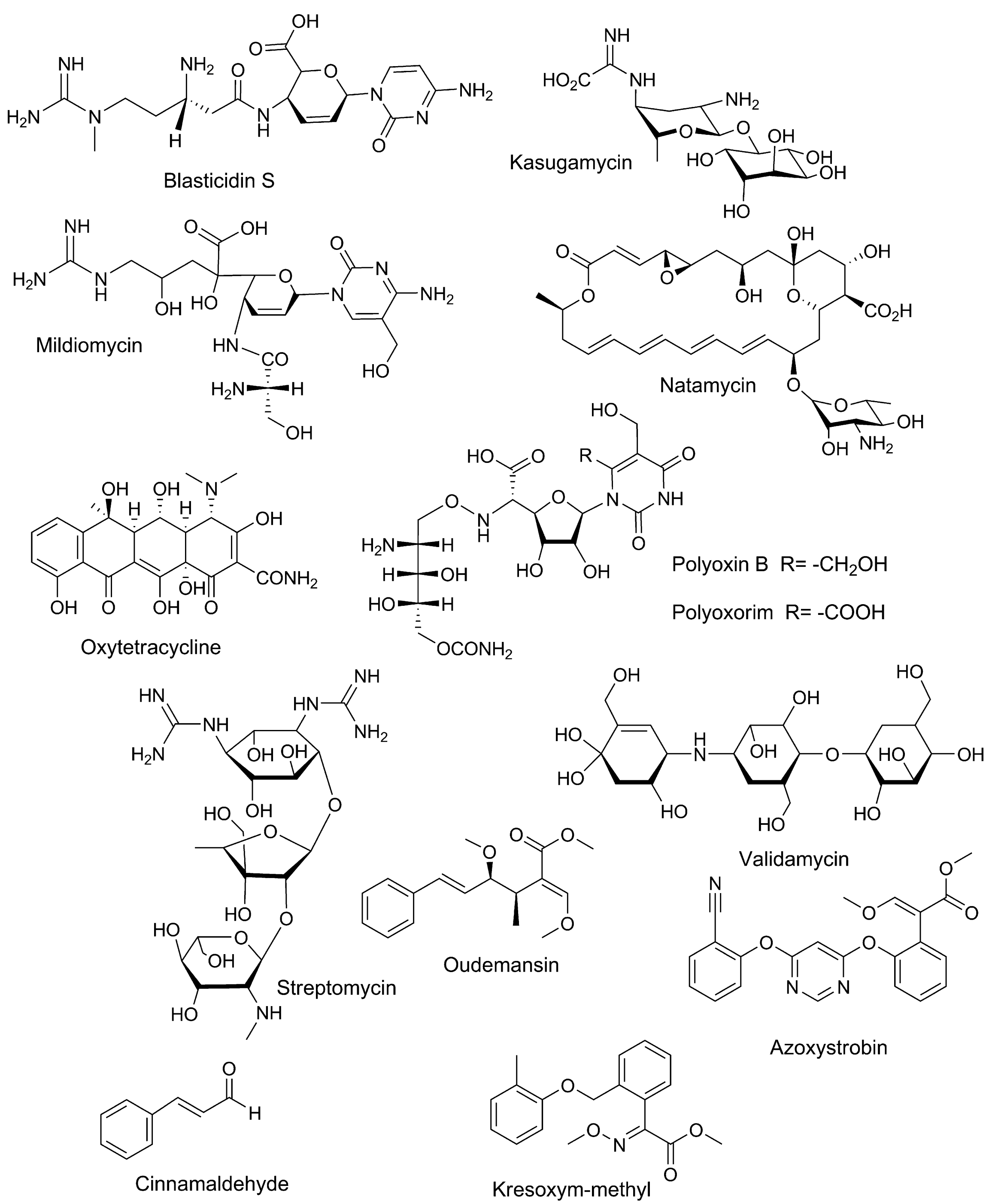

Figure 4.1. Structures of the natural fungicides and bactericides mentioned in the text.

(e.g., MyShield) that is used for control of bacterial diseases. Again, it inhibits protein synthesis by disrupting t-RNA/ribosome interactions[149] and has pharmaceutical uses.

The polyoxins (polyoxin B and polyoxorim—Fig. 4.1) from *Streptomyces cacoai* are also used as agricultural fungicides. Trade names include Polyoxin Z and Endorse for polyoxorim and Polyoxin AL for polyoxin B. These compounds may act through inhibition of fungal cell wall biosynthesis.[150]

In addition to being used as a pharmaceutical, streptomycin (Fig. 4.1) (from *Streptomyces griseus*) is used for bacterial plant diseases. It acts by interference with prokaryotic protein synthesis by binding the 30S ribosomal subunit.[151] As an agricultural fungicide, it has numerous trade names (e.g., Plantomycin, Agrimycin, Agrept, AAstrepto, and BacMaster) Resistance to it is widespread. It sometimes causes chlorosis to plants by interference with plastid protein synthesis.[152]

Finally, validamycin (Fig. 4.1) (e.g., Validacin™, Valimun™, Sheathmar™, Mycin™) from *S. hygroscopicus* is used for *Rhizoctonia* spp. control on a variety of crops. It inhibits trehalase,[153] an enzyme necessary to fungi for generation of glucose to growing hyphal tips. Knocking out this enzyme stops growth, so the compound is essentially fungistatic.

4.2.2. Chitin components

Chitin (*N*-acetylchitosan) and chitosan (poly-D-glucosamine) are found in fungal cell walls and arthropod exoskeletons. Chitosan is an effective elicitor of SAR to pathogens, including phytoalexin synthesis, in plants.[154] Presumably, plants have evolved a receptor/signally system to sense fungal pathogens in order to initiate chemical warfare with them. Preparations of chitin/chitosan from both crustacean exoskeletons (e.g., Elexa™, a 4% aqueous suspension)[155] and dried yeast (*Saccharomyces* cerevisisae) hyrdrolysate (KeyPlex™) are sold as fungicides. The latter product is combined with other ingredients. How much of the fungicidal effect of chitosan is due to induction of resistance mechanisms of the crop is difficult to separate from possible direct fungicidal effects as chitosan possess some direct fungicidal activity.[156]

4.2.3. Cinnamaldehyde

Cinnamaldehyde (Fig. 4.1) is found in several plants, but seeds of the weed *Cassia obtusifolia* are especially rich in it. It is usually synthesized chemically for use as an agricultural fungicide (e.g., Vertigo™, Cinnacure™) on a variety of crops. Its mode of action is apparently though inhibition of synthesis of the fungal cell wall component chitin.[157,158]

4.2.4. Harpin proteins

The plant pathogen *Erwinia amylovora* that causes fire blight in apples and pears produces a 40 kD protein termed 'harpin protein' that induces SAR in plants.[159,160] It is produced by heterologous expression of the gene for this protein from *E. amylovora* in *Escherichia coli*. Since it induces SAR, it decreases susceptibility to a broad range of fungal, bacterial, and viral diseases, as well as to nematodes. Harpin protein is sold as a 3% formulation (Messenger™). Harpin αβ (ProAct™) is a protein consisting of four fragments of other harpin proteins. It is also an elicitor of SAR.

4.2.5. Laminarine

This product (Iodus™) is a preparation of the storage polysaccharide (a β-1,3-glucan with some β-1,6-linked branches) of the brown alga *Laminaria digitata*. It is an elicitor of SAR and not a true fungicide.[161]

4.2.6. Extract of *Macleaya cordata*

An extract of the plant *M. cordata* is sold as a fungicide (Qwel™). Its greenhouse activity is comparable to synthetic fungicides.[162] The preparation contains numerous alkaloids, but it may be acting through induction of SAR.

4.2.7. Strobilurins

Strobilurin and the related antifungal oudemansin (Fig. 4.1) are produced by basidiomycetes that colonize dead wood. These compounds, which provide an advantage over competing fungi, have served as lead structures for commercialized synthetic analogs such as azoxystrobin and kresoxym-methyl (Fig. 4.1). These compounds inhibit mitochondrial respiration by blocking the ubiquinone receptor.[163] Resistance to this class of fungicides has already evolved.[164]

5. Conclusions

Conventional pest management has been significantly influenced by bioactive natural products that are used directly, or in a derived form, as pesticides. Biobased pesticides are commonly used as alternatives to synthetic compounds in organic agriculture. While some of these insecticidal and fungicidal compounds have transferred successfully in the more conventional crop production systems, good natural herbicides have been lacking. The only natural herbicide available for large-scale cropping system is glufosinate (a metabolite of bialaphos), although it is not accepted by organic farmers. However, glufosinate and all of the commercially available natural herbicides (e.g., corn gluten meal, acetic acid, essential oils) are non-selective and require careful application in order to preserve the crop of interest. Under particular cropping systems, allelopathy may be able to contribute to weed control. These past successes and the current public's concern over the impact of synthetic pesticides on the environment ensures a continued, if not an increased, interest in searching nature for environmentally friendlier pest management tools.

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