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Review

Natural products that have been used commercially as crop protection agents

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Abstract: Many compounds derived from living organisms have found a use in crop protection. These compounds have formed the basis of chemical synthesis programmes to derive new chemical products; they have been used to identify new biochemical modes of action that can be exploited by industry-led discovery programmes; some have been used as starting materials for semi-synthetic derivatives; and many have been used or continue to be used directly as crop protection agents. This review examines only those compounds derived from living organisms that are currently used as pesticides. Plant growth regulators and semiochemicals have been excluded from the review, as have living organisms that exert their effects by the production of biologically active secondary metabolites.

Keywords: fungicide; herbicide; insecticide; natural product; mode of action

1 INTRODUCTION

Natural products have been used for the benefit of humankind for many thousands of years, be it for food, clothing, cosmetics, construction of shelters and traps, tools and weapons, poisons for game and fish, medicines or crop protection agents. Where a physiological effect on a pest was required, early compounds were simply extracted from a source and used as an impure mixture of chemicals, one or more of which gave the required response. The science of natural products has advanced significantly in recent times, and these compounds are being used as products in their own right as pure (or at least characterised) compounds, as new chemical skeletons that can be modified by the ingenious synthesis chemist or as indicators of new, effective biochemical modes of action (increasingly important in a world of high-throughput *in vitro* screening).

A large number of volumes and reviews have been written about the use of natural products as pesticides,[1–9] each having strengths and weaknesses when considering the vast array of compounds that have found use or are currently being used in crop protection. Most of this literature deals with compounds with promising activity that are not commercially available. This review is designed to identify the natural compounds and preparations that have been characterised and have found a commercial application. In each case the source, chemistry, mode of action (where known), biological spectrum and major products will be described.

To the authors' knowledge, this is the first review of only commercially available natural pest management materials. Interest in these products for use in organic agriculture and 'green' pest management has grown substantially in recent years, enhancing the need for such a review. Not all of the products that will be discussed are still on the market. Not included will be uncharacterised mixtures, 'snake oils' and compounds without a sound scientific description of their biological effectiveness. It is true that insect semiochemicals used in pest management are natural products, but these compounds justify a review in their own right and will not be included. Also excluded will be *Bacillus thuringiensis* Berliner bacterial endotoxins and the genes that code for them, as this too is a topic so large that it justifies a review on its own. As a general rule, products that cause an increase in crop 'vigour' will not be included, as many of these are acting as complex organic fertilisers, with the observed effects being associated with the addition of nitrogen and other essential minerals. Insect-specific baculoviruses are considered to be living rather than natural products and are hence not covered by the review.

An attempt has been made to give examples of trade names of most of the generic products mentioned. This does not imply endorsement of these products over any similar products that are not mentioned, nor does it claim to be a complete list of available products. The authors have tried to include all commercial products, but they may have missed products that are not mentioned in the scientific literature. Unfortunately,

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rigorous scientific evaluations of many of the products discussed below are not available.

2 BACTERIA-DERIVED PRODUCTS

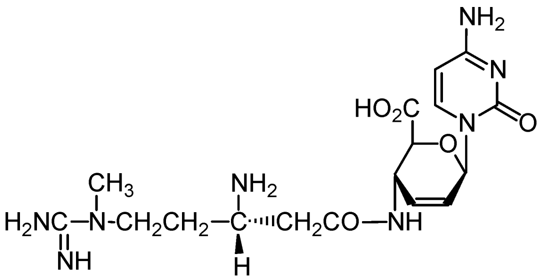
2.1 Fungicides and bactericides

2.1.1 Blasticidin-S

Blasticidin-S (JMAF) (Fig. 1) was isolated from the soil actinomycete *Streptomyces griseochromogenes* Fukunaga in 1955 by Fukunaga *et al.*,[10] and later by Takeuchi *et al.* in 1958.[11] Its fungicidal properties were first described by Misato *et al.*[12] in 1959. It is usually sold as the benzylaminobenzenesulfonic acid salt.

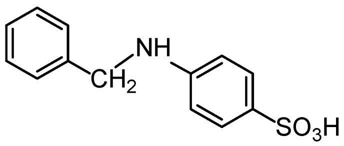
Blasticidin-S has the CAS registry number *[2079-00-7]*, although it was formerly given the codes *[11 002-92-9]* and *[12 767-55-4]*. The benzylaminobenzenesulfonic acid salt has the code *[51 775-28-1]*.

It is used to control rice blast [*Pyricularia oryzae* Cavara; perfect stage *Magnaporthe grisea* (Hebert) Barr] by foliar application. Blasticidin-S inhibits protein biosynthesis by binding to the 50S ribosome in prokaryotes (at the same site as gougerotin), leading to the inhibition of peptidyl transfer and protein chain elongation.[13] It is a contact fungicide with protective and curative action, exhibiting a wide range of inhibitory activity on the growth of bacterial and



Blasticidin S

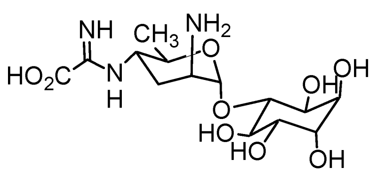
1-(4-amino-1,2-dihydro-2oxopyrimidin-1-yl)-4-[(*S*)-3-amino-5-(1-methylguanidino)valeramido]-1,2,3,4-tetradeoxy-β-D-erythro-hex-2-enopyranuronic acid



benzylaminobenzenesulfonic acid

MSLNTSLGASTMQISTGGAGGNNGLLGTSRQNAGLGGNSALGLGGGNQNDTVNQ
LAGLLTGMMMMMSMMGGGGLMGGGLGGGLGNGLGGSGGLGEGLSNALNDMLG
GSLNTLGSKGGNNTTSTTNSPLDQALGINSTSQNDDSTSGTDSTSDSSDPMQQLLK
MFSEIMQSLFGDGGDTQGSSSGGKQPTEGEQNAYKKGVTDALSGLMGNGLSQLL
GNGGLGGGQGGNAGTGLDGSSLGGKGLRGLSGPVDYQQLGNAVGTGIGMKAGIQ
ALNDIGTHRHSSTRSFVNKGDRAMAKEIGQFMDQYPEVFGKPQYQKGPGQEVKTD
DKSWAKALSKPDDDGMTPASMEQFNKAKGMIKRPMAGDTGNGNLHDAVPVVLRW
VLMP

Deduced amino acid sequence of harpin



Kasugamycin: 1L-1,3,4/2,5,6-1-deoxy-2,3,4,5,6-pentahydroxycyclohexyl 2-amino-2,3,4,6-tetradeoxy-4-(α-iminoglycino)-α-D-*arabino*-hexopyranoside

Figure 1. Bacteria-derived fungicides and bactericides.

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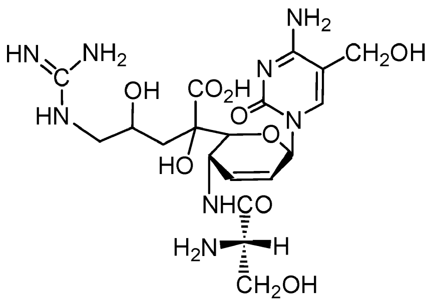
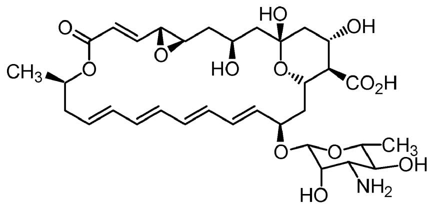
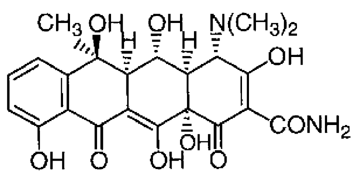


Mildiomycin: (2*R*,4*R*)-2-{(2*S*,3*S*,6*R*)-6-[4-amino-1,2-dihydro-5-(hydroxymethyl)-2-oxopyrimidin-1-yl]-3,6-dihydro-4-(L-serylamino)-2*H*-pyran-2-yl}-2,4-dihydroxy-5-guanidinopentanoic acid



Natamycin: (8*E*,14*E*,16*E*,18*E*,20*E*)-(1*R*,3*S*,5*R*,7*R*,12*R*,22*R*,24*S*,25*R*,26*S*)-22-(3-amino-3,6-dideoxy-β-D-mannopyranosyloxy)-1,3,26-trihydroxy-12-methyl-10-oxo-6,11,28-trioxatricyclo[22.3.1.0^{5,7}]octacosa-8,14,16,18,20-pentaene-25-carboxylic acid



Oxytetracycline: (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide

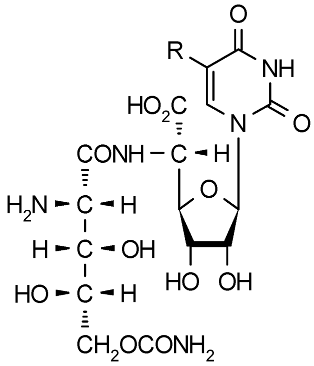
Figure 1. Continued.

fungal cells. In addition, it has been shown to have antiviral and antitumour activity. It inhibits spore germination and mycelial growth of *P. oryzae* in the laboratory at rates below 1 mg mL^{-1}. It is sold as dustable powder (DP), emulsifiable concentrate (EC) and wettable powder (WP) formulations under the trade name Bla-S by Kaken, Kumiai and Nihon Noyaku. For control of rice blast it is used at rates between 100 and 300 g AI ha^{-1} by foliar application. Damage can be caused to alfalfa, aubergines, clover, potatoes, soybean, tobacco and tomatoes. Excessive application produces yellow spots on rice leaves. In recent years, its significance as a fungicide has decreased following the introduction of new, lower-toxicity, pathogen-specific, synthetic rice blast products.

Blasticidin-S is relatively toxic to mammals, with the acute oral LD_{50} to rodents being below 100 mg kg^{-1}, but the acute dermal LD_{50} to rats is >500 mg kg^{-1}. It is also a severe eye irritant. It is relatively non-hazardous to non-target organisms when used as labelled and has no deleterious effects on the environment.

2.1.2 *Harpin protein*

Harpin protein is produced by *Erwinia amylovora* (Burrill) Winslow, a bacterium that causes the disease fire blight in apples and pears. Harpin is an acidic, heat-stable, cell envelope-associated protein with a molecular mass of about 40 kD (Fig. 1). The protein consists of 403 amino acid residues with no cysteine. It is produced commercially in a weakened strain of *Escherichia coli* (Migula) Castellani & Chalmers

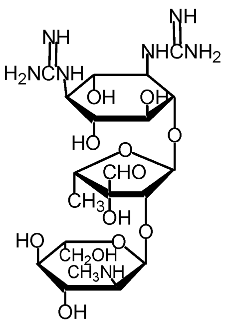


polyoxin B: R = – CH_2OH

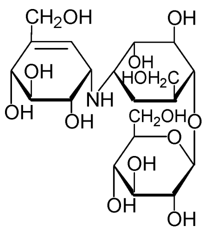
polyoxorim: R = – CO_2H

Polyoxin B: 5-(2-amino-5-*O*-carbamoyl-2-deoxy-L-xylonamido)-1,5-dideoxy-1-(1,2,3,4-tetrahydro-5-hydroxymethyl-2,4-dioxopyrimidin-1-yl)-β-D-allofuranuronic acid

Polyoxorim: 5-(2-amino-5-*O*-carbamoyl-2-deoxy-L-xylonamido)-1-(5-carboxy-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-1-yl)-1,5-dideoxy-β-D-allofuranuronic acid



Streptomycin: *O*-2-deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-formyl-α-L-lyxofuranosyl-(1→4)-*N*^{1},*N*^{3}-diamidino-D-streptamine and 1,1'-[1-L-(1,3,5/2,4,6)-4-[5-deoxy-2-*O*-(2-deoxy-2-methylamino-α-L-glucopyranosyl)-3-*C*-formyl-α-L-lyxofuranosyloxy]-2,5,6-trihydroxycyclohex-1,3-ylene]diguanidine



Validamycin: 1L-(1,3,4/2,6)-2,3-dihydroxy-6-hydroxymethyl-4-[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enylamino]cyclohexyl β-D-glucopyranoside

Figure 1. Continued.

by transfer of the DNA fragment encoding harpin protein from *E. amylovora* to the cell production strain *E. coli* K-12.[14] This harpin-producing isolate is considered to be a debilitated, non-pathogenic, nutritionally deficient bacterial isolate of *E. coli* that cannot grow in the human digestive tract or survive in the environment.

A broad range of fungal, bacterial and viral disease organisms are controlled by harpin, including bacterial leaf spot [*Xanthomonas campestris* (Pammell) Dowson], bacterial speck (*Pseudomonas syringae* Van Hall), bacterial wilt [*Pseudomonas solanacearum* (Smith) Smith], Fusarium wilt, Phytophthora root rot, rice stem rot [*Magnaporthe salvinii* (Cattaneo) Krause & Webster], sheath blight [*Rhizoctonia solani* Kühn (*Pellicularia sasakii* Ito)], apple scab [*Venturia inaequalis* (Cooke) Winter], fire blight (*E. amylovora*), Botrytis bunch rot, black rot [*Guignardia bidwellii* (Ellis) Viala & Rivas], black leaf spot (*Diplocarpon rosae* Wolf), cucumber mosaic virus, root-knot nematodes (*Meloidogyne* spp.), tobacco cyst nematode (*Globodera solanacearum* Miller & Gray) and tobacco mosaic virus (TMV). It provides significant plant growth enhancement and, thereby, suppression of some insects. Growth enhancements may include improved germination, increased overall plant vigour, accelerated flowering and fruit set, advanced maturity and increased yield and quality of the final harvest. It can be used on a broad range of crops both outdoors and protected, including traditional field crops, minor use crops, turf and ornamentals. Harpin protein has been approved for use on tomatoes to enhance uniformity, size and yield, and on citrus to increase fruit set and yield.

Harpin does not act directly on the disease organism, but instead activates a natural defence mechanism in the host plant, referred to as systemic acquired resistance (SAR).[14] Harpin is effective against certain viral diseases for which there are no other controls or resistant plant varieties. It also protects against soil-borne pathogens and pests, such as certain nematodes and fungal diseases, that have few effective controls except for methyl bromide. Because harpin exhibits no direct inhibitory or toxic effect on plant pathogens, it is claimed that it cannot exert the selection pressure that would promote the development of resistance in pest populations. By decreasing the use of conventional pesticides, harpin is expected to be an important tool in resistance management programmes.

The product Messenger is an end-use product formulation containing 3% harpin protein, formulated as a water-dispersible granule (WG) and commercialised by Eden Bioscience.

The end-use product may be applied preplanting or as a foliar spray with conventional ground or aerial spray equipment or by conventional irrigation/chemigation systems. In addition, it may be used as a seed treatment or in glasshouses as a soil drench. Use rates are very low, generally 5–25 g AI ha^{-1} applied at 14 day intervals. Glasshouse drench applications should be made 3 weeks after seeding, with a second application 5–7 days before transplanting. Field foliar applications are recommended at planting and at 14 day intervals until harvest. For newly seeded crops, sprays should begin at the appearance of the first true leaf.

Harpin is not considered to be a toxic pesticide. Harpin protein is classified as a toxicity category IV product by the US-EPA via the oral, dermal and inhalation route, and a toxicity category IV eye and skin irritant. Harpin is not expected to cause any harm to the environment because it is applied at low rates and degrades rapidly after application, and it poses little or no concern as a ground or surface water contaminant. In addition, it has no demonstrable adverse effects on birds, fish, aquatic invertebrates, honey bees, non-target plants and algae. Therefore, risks to wildlife and beneficial insects are expected to be minimal.

Harpin $\alpha\beta$ is a protein that consists of four fragments from other harpin proteins. For commercial production of the proteins, the DNA sequences coding for harpin $\alpha\beta$ were put into a weakened strain of *Escherichia coli* (*E. coli* K-12). This genetically modified *E. coli* K-12 produces large amounts of harpin $\alpha\beta$, which is then isolated and purified from the bacterial growth medium. Harpin $\alpha\beta$ is effective in controlling a wide range of fungal, bacterial and viral plant pathogens in the growing plant, with these effects continuing post-harvest. It also reduces infestation by selected insect and nematode pests. It provides the same plant germination, growth and yield enhancement as other harpins discussed above.

Harpin $\alpha\beta$ proteins can be used on a broad range of crops both outdoors and protected, including traditional field crops, minor use crops, turf and ornamentals.

Harpin $\alpha\beta$ acts in an identical fashion to harpin protein (see above). ProAct is an end-use product formulation containing 1% harpin $\alpha\beta$ protein, formulated as a WG and sold by Eden Bioscience.

Harpin $\alpha\beta$ protein, like harpin, is not expected to have any adverse effects on humans or non-target organisms. Eden Bioscience continues to develop harpin-like proteins with a variety of pest and disease spectra and different methods of application. The harpin group of crop protection agents is newly introduced and is showing a slow but steady increase in use by commercial growers. Eden Bioscience Corp has signed an asset purchase agreement to sell the company's harpin protein technology and substantially all of the assets related to its agricultural and horticultural markets to Plant Health Care Inc (PHC), a subsidiary of Plant Health Care plc.

2.1.3 Kasugamycin

Kasugamycin (JMAF) (Fig. 1) and kasugamycin hydrochloride hydrate were isolated from the soil actinomycete *Streptomyces kasugaensis* Hamad *et al.* and were first described by Umezawa *et al.* in 1965[15] and introduced by Hokko Chemical Industry Co. Ltd.

The CAS registry numbers are *[6980-18-3]* and *[19 408-46-9]*. The product is sold as the hydrochloride.

The biological activity of these compounds was first described by Hamada *et al.*[16] in 1965. Kasugamycin is recommended for the control of rice blast (*P. oryzae*; perfect stage *M. grisea*) in rice, leaf spot in sugar beet and celery (*Cercospora* spp.), bacterial disease in rice and vegetables and scab (*Venturia* spp.) in apples and pears.

They inhibit protein biosynthesis by interfering with the binding of aminoacyl-tRNA to both the mRNA-30S and the mRNA-70S ribosomal subunit complexes, thereby preventing the incorporation of amino acids into proteins.[17] Kasugamycin is a systemic fungicide and bactericide with both protectant and curative properties. Resistance to kasugamycin was detected within 3 years of its introduction in 1965, and by 1972 it had become a serious problem in Japanese rice fields. Today, mixtures of kasugamycin with other fungicides with different modes of action are used. Resistant strains of *P. oryzae* are less fit than susceptible strains and, once applications of kasugamycin are discontinued in the field, the level of resistance declines rapidly. Kasugamycin inhibits hyphal growth of *P. oryzae* on rice, preventing lesion development; it is a comparatively weak inhibitor of spore germination, appressorium formation and penetration into the epidermal cells. In contrast, against *Fulvia fulva* (Cooke) Cif. on tomatoes, inhibition of sporulation is high, but its effects on hyphal growth are poor. Kasugamycin is taken up by plant tissue and is translocated.

Kasugamycin hydrochloride hydrate is sold as WP, DP, soluble concentrates (SL) and granule (GR) formulations under the trade names Kasugamin, Kasumin and Kasu-rab-valida-sumi (plus fthalide plus validamycin plus fenitrothion) from Hokko. It is applied as a foliar spray, a dust or a seed treatment at rates from $20\,\mathrm{g\,AI\,L^{-1}}$. There has been evidence of slight phytotoxicity on crops such as peas, beans, soybeans, grapes, citrus and apples. No injury has been found on rice, tomatoes, sugar beet, potatoes and many other vegetables. The use of kasugamycin has declined following the rapid onset of resistance and the release of new, disease-specific chemical fungicides for rice blast control.

As with other aminoglycoside antibiotics, kasugamycin is not considered to be toxic to mammals and there is no evidence that it has had any adverse effects on non-target organisms or on the environment.

2.1.4 *Mildiomycin*

Mildiomycin (JMAF) (Fig. 1) was isolated from the soil actinomycete *Streptoverticillium rimofaciens* strain B-98 891 and first reported by Harada and Kishi;[18] its fungicidal properties were reported by Kusaka *et al*. in 1979.[19]

Mildiomycin has the CAS registry number *[67 527-71-3]*, although it was formerly coded *[57 497-78-6]* and *[67 983-11-3]*. It is used to control powdery mildews [*Erysiphe* spp., *Uncinula necator* (Schwein) Burrill, *Podosphaera* spp. and *Sphaerotheca* spp.] in ornamentals.

The mode of action of mildiomycin is believed to be inhibition protein biosynthesis in fungi by blocking peptidyl-transferase.[20] In the field, it is effective as an eradicant, with some systemic activity. Mildiomycin is specifically active against the pathogens that cause powdery mildew and is much less effective against bacteria.

It is sold as a WP formulation under the trade name Mildiomycin by Sumitomo Chemical Takeda. Rates of use to eradicate infection and offer subsequent protection are from 50 to $100\,\mathrm{mg\,L^{-1}}$. Mildiomycin has not been widely used for disease control outside Japan.

Mildiomycin has very low mammalian toxicity and it has not been shown to have any adverse effects on non-target organisms or the environment.

2.1.5 *Natamycin*

Natamycin (BAN) (Fig. 1) (also known as myprozine, pimaricin and tennectin) is a secondary metabolite of the actinomycetes *Streptomyces natalensis* Struyk, Hoette, Drost, Waisvisz, Van Eek & Hoogerheide and *S. chattanoogensis* Burns & Holtman. Its structure was established by Golding *et al*.[21] and Meyer,[22] and its stereochemistry was revised by Lancelin and Beau[23] and Duplantier and Masamune.[24] It was introduced as a fungicide by Gist-Brocades NV. Natamycin has the CAS registry number *[7681-93-8]*.

It is used to control various fungal diseases, but especially basal rots on ornamental bulbs such as daffodils that are caused by *Fusarium oxysporum* Schlecht. It is usually applied as a dip in combination with a hot water treatment prior to planting. Its precise mode of action is not known. Natamycin was sold as a WP under the trade name Delvolan, but is now withdrawn.

Natamycin is not toxic to mammals or fish and is readily biodegradable.[25,26] No adverse effects have been observed on non-target organisms or on the environment.

2.1.6 *Oxytetracycline*

Oxytetracycline [E-ISO, (*f*) F-ISO, BSI, JMAF, BAN] (Fig. 1) is produced by the soil actinomycete *Streptomyces rimosus* Sobin *et al*. and usually sold as the hydrochloride. It was first described by Finlay *et al*.[27] Oxytetracycline has CAS registry numbers *[79-57-2]* and *[2058-46-0]* for the hydrochloride.

Oxytetracycline is used to control bacterial diseases such as fireblight (*E. amylovora*) and diseases caused by *Pseudomonas* and *Xanthomonas* species,[28] and it is also effective against diseases caused by mycoplasma-like organisms. It is used in stone and pome fruit and in turf.

Oxytetracycline is a potent inhibitor of protein biosynthesis in bacteria.[29] It binds to the 30S and 50S bacterial ribosomal subunits and inhibits the binding of aminoacyl-tRNA and the termination factors RF1 and RF2 to the A site of the bacterial ribosome. It is much less active in mammalian systems. It is rapidly taken up by plant leaves, particularly through stomata, and is readily translocated to other plant tissues. It is an effective antibacterial and is often mixed with streptomycin to prevent the development of streptomycin resistance. Oxytetracycline is sold as a water-soluble powder (SP) under a wide variety of trade names including Mycoshield (calcium salt) from Syngenta, Cuprimicina Agrícola, Cuprimicín 100 (plus streptomycin) and Cuprimicín 500 [plus streptomycin plus copper sulfate (tribasic)] from Ingeniería Industrial, Mycoject (calcium salt) from Mauget and Phytomycin (plus streptomycin sulfate) from Ladda. It is applied as a foliar spray to infected plants. Oxytetracycline is used as a pharmaceutical where its better absorption profile makes it preferable to tetracycline for moderately severe acne, and it is sometimes used to treat spirochaetal infection, clostridial wound infection and anthrax in patients sensitive to penicillin. Oxytetracycline is used to treat infections of the respiratory and urinary tracts, skin, ear and eye, and gonorrhoea. Oxytetracycline is especially valuable in treating non-specific-urethritis, *Lymphogranuloma venereum*, Lyme disease, brucellosis, cholera, plague, typhus, relapsing fever, tulaeraemia and infections caused by *Chlamydia* spp., Mycoplasma spp. and *Rickettsia* spp. Oxytetracycline can be used to control the outbreak of American foulbrood and European foulbrood in honey bees. Its use as a crop protection agent is declining.

Oxytetracycline is considered to be non-toxic to mammals and has not been shown to have any adverse effects on non-target organisms or on the environment.

2.1.7 The polyoxins

The fungicidal polyoxins are polyoxin B (JMFA) and polyoxorim (BSI, pa ISO) (Fig. 1). Polyoxin B is one of the secondary metabolites produced by the fermentation of the soil actinomycete *Streptomyces cacoai* var *asoensis* Isono *et al*. It was first isolated by Isono *et al*[30] in 1965 and was introduced as a commercial fungicide by Hokko Chemical Industry Company Ltd, Kaken Pharmaceutical Company Ltd, Kumiai Chemical Industry Company Ltd and Nihon Nohyaku Company Ltd. Polyoxorim (polyoxin D) was isolated by Suzuki *et al*.[31] and Isono *et al*.[32] The zinc salt was introduced as a fungicide by Kaken Pharmaceutical Company Ltd, Kumiai Chemical Industry Company Ltd and Nihon Nohyaku Company Ltd.

Polyoxin B has the CAS registry number *[19 396-06-6]*. Polyoxorim has the CAS registry number *[22 976-86-9]* and the zinc salt is coded *[146 659-78-1]*. The family of antifungals has the CAS registry number *[11 113-80-7]*.

Polyoxin B is used to control a range of plant pathogenic fungi such as *Sphaerotheca* spp. and other powdery mildews, *Botrytis cinerea* Pers., *Sclerotinia sclerotiorum* De Bary, *Corynespora melonis* Lindau, *Cochliobolus miyabeanus* (Ito & Kuribay) Drechsler ex Dastur, *Alternaria alternata* (Fr.) Keissler and other *Alternaria* species in vines, apples, pears, vegetables and ornamentals. The primary use of polyoxorim is for the control of rice sheath blight, *R. solani*. It is also effective against apple and pear canker [*Nectria galligena* Bresadola (*Diplodia pseudodiplodia* Fuckel)] and *Drechslera* spp., *Bipolaris* spp., *Curvularia* spp. and *Helminthosporium* spp., with the major use being in rice, although it also has applications in pome fruit and turf.

Polyoxins cause a marked abnormal swelling on the germ tubes of spores and hyphal tips of the pathogen, rendering the treated fungus non-pathogenic. In addition, the incorporation of [^{14}C]glucosamine into cell-wall chitin of *C. miyabeanus* is inhibited. Polyoxins apparently exert their effects through inhibition of cell wall biosynthesis.[33,34] They are systemic fungicides with protective action. Polyoxin B is effective at controlling a variety of fungal pathogens, but is ineffective against bacteria and yeasts. It is particularly effective against pear black spot and apple cork spot (*Alternaria* spp.), grey moulds (*B. cinerea*) and other sclerotia-forming plant pathogens. Resistance to polyoxin B has been found in *A. alternata* in some orchards in Japan following intensive treatment. This resistance is due to lowered penetration of polyoxin B through the fungal cell membrane and, therefore, to the site of action. Polyoxorim has good activity against rice sheath blight when applied as a foliar spray at rates of about 2 g L^{-1}. High-volume sprays on turf are effective at controlling many fungal pathogens, but not members of the Phycomycetes (no chitin in the cell wall). Polyoxorim can be used to control apple and pear canker when applied as a paste. It is also ineffective against bacteria and yeasts.

The polyoxins are sold as WP, EC, water-soluble granule (SG) and paste (PA) formulations. Polyoxin B is sold under a variety of trade names including Polyoxin AL by Kaken, Kumiai, Nihon Nohyaku and Hokko and Polybelin [plus iminoctadine tris(albesilate)] by Kumiai. Polyoxorim trade names include Endorse, Polyoxin Z (the zinc salt) and Stopit from Kaken. Crops are treated by foliar spay as soon as symptoms appear. The high incidence of evolved resistance limits the value of these compounds in crop protection.

All members of this chemical family have low mammalian toxicity and have not been shown to have any adverse effects on non-target organisms or the environment.

2.1.8 Streptomycin

Streptomycin (BSI, E-ISO, BAN, JMAF) (Fig. 1) was isolated from the soil actinomycete *Streptomyces griseus* (Krainsky) Waksman & Henrici, being first reported by Schatz *et al*.[35] in 1944; its structure was elucidated in 1947 by Kuehl *et al*[36] and Wolfrom *et al*.[37] It was first commercialised for use in crop protection by Meiji Seika Kaisha Ltd. It has the CAS registry numbers *[57-92-1]* and *[3810-74-0]* for the sesquisulfate.

Streptomycin is used for the control of bacterial shot-hole, bacterial rots, bacterial canker, bacterial wilts, fire blight and other bacterial diseases (especially those caused by gram-positive species of bacteria). It is particularly effective against *Xanthomonas oryzae* Dowson, *X. citri* Dowson, *Pseudomonas tabaci* Stevens and *P. lachrymans* Carsner, and is recommended for use in pome fruit, stone fruit, citrus fruit, olives, vegetables, potatoes, tobacco, cotton and ornamentals.

Streptomycin inhibits protein biosynthesis by binding to the 30S ribosomal subunit and causing a misreading of the genetic code in protein biosynthesis.[38] It is a bactericide with systemic action. Resistance to streptomycin is widespread, reducing the value of the compound in today's crop protection markets, and its pharmaceutical uses are now restricted to treatment of tuberculosis in admixture with other antibacterials. Streptomycin and its sesquisulfate are sold as WP and SL under a wide variety of trade names. Streptomycin's trade names as agricultural products include AAstrepto by Bayer CropScience, Cuprimicín 17 by Ingeniería Industrial, Paushamycin by Paushak, Plantomycin by Aries and Streptrol by Agtrol and Nufarm Americas. Streptomycin sesquisulfate trade names include Agrept by Meiji Seika and Agrimycin 17 and AS-50 by Syngenta and Bac-Master by Amvac. Mixtures include Cuprimicín 100 (streptomycin plus oxytetracycline) and Cuprimicín 500 [streptomycin plus copper sulfate (tribasic) plus oxytetracycline] from Ingeniería Industrial, Dustret (streptomycin sesquisulfate plus maneb) by Agsco and Seed Treatment for Potatoes (streptomycin sesquisulfate plus maneb) by Helena. They are used as foliar sprays at rates of $2\,\mathrm{g\,AI\,L^{-1}}$. Recommended use rates can cause chlorosis to rice, grapes, pears, peaches and some ornamentals, but these symptoms can be relieved by the addition of iron chloride or iron citrate to the spray tank. Streptomycin is often used in collaboration with a bactericide with a different mode of action (such as oxytetracycline) to reduce the likelihood of evolution of resistance. The market for streptomycin is relatively small, but consistent.

As with all aminoglycoside antibiotics, streptomycin has very low mammalian toxicity (sufficient to be used as a pharmaceutical), and it has not been shown to have any adverse effects on non-target organisms or the environment.

2.1.9 Validamycin

Validamycin (JMAF) (Fig. 1) (also known as validamycin A) was isolated from the soil actinomycete *Streptomyces hygroscopicus* (Jensen) Waksman & Henrici isolate *limoneus*. Its biological activity was described by Horii *et al*.[39] Validamycin has the CAS registry number *[37 248-47-8]*.

It is used for the control of *R. solani* and other *Rhizoctonia* species in rice, potatoes, vegetables, strawberries, tobacco, ginger, cotton, rice, sugar beet and other crops. Validamycin is non-systemic, but has a fungistatic action, showing no fungicidal action against *R. solani*, but causing abnormal branching of the tips of the pathogen followed by a cessation of further development.[40] Validamycin has a potent inhibitory activity against trehalase in *R. solani* AG-1, without any significant effects on other glycohydrolytic enzymes tested.[41] Trehalose is well known as a storage carbohydrate in the pathogen, and trehalase is believed to play an essential role in the digestion of trehalose and transport of glucose to the hyphal tips.

Very low rates of use give excellent control of *R. solani* in various crops, and rates of $0.3\,\mathrm{g\,AI\,L^{-1}}$ give effective control of rice sheath blight. It is applied as a foliar spray, a soil drench, a seed treatment or by soil incorporation. It is sold as DP, SL, powder seed treatment (DS) and liquid formulations under a wide variety of trade names including Validacin, Valimun, Dantotsupadanvalida (plus cartap hydrochloride plus clothianidin) and Hustler (plus cartap hydrochloride plus clothianidin plus ferimzone plus fthalide) by Sumitomo Chemical Takeda, Sheathmar by Sumitomo Chemical Takeda and Dhanuka, Mycin by Sanonda, Rhizocin by Nagarjuna Agrichem, Solacol by Bayer CropScience, Valida by Nichimen, Kasu-rab-valida-sumi (plus fenitrothion plus kasugamycin plus fthalide) and Kasu-rab-validatrebon [plus etofenprox plus kasugamycin hydrochloride hydrate plus fthalide)] by Hokko and Vivadamy and Vimix (plus 1-naphthylacetic acid plus 2-naphthyloxyacetic acid) by Vipesco. Concentrations as high as $1\,\mathrm{g\,L^{-1}}$ showed no phytotoxicity to over 150 different target crops. Validamycin continues to find wide usage in a wide variety of crops, particularly in Japan.

Validamycin is not considered to be toxic to mammals and has no adverse effects on non-target organisms or on the environment.

2.2 Herbicides

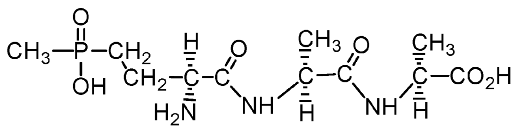
2.2.1 Bilanafos

The tripeptide herbicide bilanafos (Fig. 2) was originally isolated from the soil-inhabiting actinomycete *S. hygroscopicus*, and was introduced as a herbicide produced by fermentation by Meiji Seika.[42,43] It is also produced by *S. viridochromeogenes* (Krainsky) Waksman & Henrici.[44]

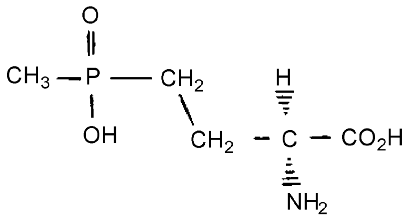
Its common names are bilanafos (BSI, draft E-ISO, (*m*) draft F-ISO) and bialaphos (JMAF), although it is also known as bilanaphos, phosphinothricyl-alanyl-alanine and phosphinothricin-alanyl-alanine. The CAS registry numbers are *[35 597-43-4]* for bilanafos and *[71 048-99-2]* for bilanafos-sodium. It was introduced as a herbicide in Japan in 1984 – the first herbicide to be produced by fermentation.

Bilanafos is used post-emergence in vines, apples, brassicas, cucurbits, mulberries, azaleas, rubber and many other crops, on uncultivated land for the post-emergence control of annual weeds in crop situations and for control of annual and perennial weeds on uncultivated land.

Bilanafos itself is not directly phytotoxic, but must be metabolically converted by the target plant to the actual phytotoxin, phosphinothricin {4-[hydroxy(methyl)phosphinoyl]-L-homoalanine} (Fig. 2), a potent irreversible inhibitor of glutamine synthetase (GS) (reviewed by Lydon and Duke[45]). Phosalacine is a phytotoxic bialanafos tripeptide analogue that also contains phosphinothricin,[46] but it is not sold as a herbicide. Glufosinate-ammonium, the monoammonium salt of the synthesised version of phosphinothricin, was introduced by Hoechst (now Bayer CropScience) as a non-selective herbicide under several trade names (e.g. Basta, Ignite and Liberty). The synthesised version is a racemic mixture of the ammonium salts of phosphinothricin and its D-enantiomer that is sold in liquid formulations with $120-200\,\mathrm{g\,AI\,L^{-1}}$. Other names for phosphinothricin include (*S*)-phosphinothricin, L-glufosinate, phosphinothricine and *S*-glufosinate.



Bilanafos: 4-[hydroxy(methyl)phosphinoyl]-L-homoalanyl-L-alanyl-L-alanine



L-Phosphinothricin : 4-[hydroxyl(methyl)phosphinoyl]-L-homoalanine

Figure 2. Bacteria-derived herbicides.

The synthesised racemic mixture of free acids is known as (±)-phosphinothricin, 3-amino-3-carboxypropylmethylphosphinic acid, DL-2-amino-4-(methylphosphino)butanoic acid, DL-phosphinothricin, glufosinate and HOE 35 956. The CAS registry number of phosphinothricin is *[35 597-44-5]*, that of the synthesised racemic mixture is *[51 276-47-2]* and that of the ammonium salt of the mixture is *[77 182-82-2]*. Since glufosinate is not strictly a natural product and is produced by chemical synthesis, it is not used by organic farmers.

Inhibition of GS causes ammonia accumulation and rapid inhibition of photorespiration. The effects of bilanafos and phosphinothricin on plants are too rapid to be due to starvation for glutamine and other amino acids derived from glutamine. The rapid phytotoxic response was originally thought to be due to the high ammonium ion levels. However, the effects of the herbicide can be reversed by supplying the plant with glutamine, and this does not reduce the levels of ammonium ions. Most of the phytotoxicity of inhibiting glutamine synthetase in C_3 plants is due to rapid cessation of photorespiration, resulting in accumulation of glyoxylate in the chloroplast and rapid inhibition of ribulose bisphosphate carboxylase. Inhibition of carbon fixation in the light leads to a series of events that ends with severe photodynamic damage. Several other natural inhibitors of GS have been discovered, but none is as herbicidally active as phosphinothricin.[45] None of these compounds has been commercialised.

Phosphinothricin is not rapidly degraded metabolically within higher plant tissue and is readily moved throughout treated plants in both the xylem and the phloem. The producing organism possesses an enzyme, phosphinothricin acetyl transferase (pat), that acetylates the herbicide, rendering it non-inhibitory to GS and, hence, not phytotoxic. The gene that encodes this enzyme [*pat* or *bar* (bilanafos resistance) gene] has been used to transform several crop plants to render them resistant to foliar applications of bilanafos and its synthetic analogue, glufosinate. Glufosinate-resistant cotton, maize and canola are grown in North America.

Because bilanafos is metabolically converted into phosphinothricin, which then strongly inhibits GS, control of treated vegetation is considered non-selective, although there is a wider range of susceptibility than with glyphosate. Herbicidal effects often take several days to develop, and death may take as long as 14–21 days. Regrowth of deep-rooted perennials may occur, and retreatment may be necessary. Bilanafos has no effects pre-emergence.

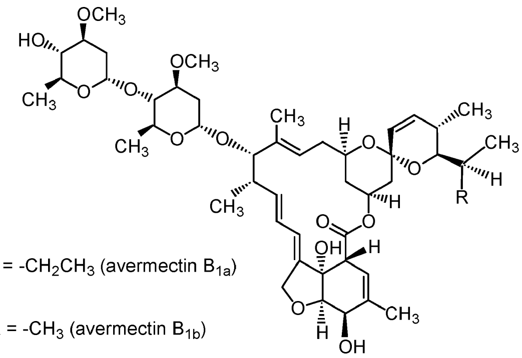
Bilanafos is sold as SP and liquid formulations under the trade name Herbiace (introduced by Meiji Seika in 1988). It is applied post-emergence at rates of 0.9–1.8 kg AI ha^{-1} for control of annual weeds and at higher rates for control of perennial weeds. When applied post weed emergence in crop situations, it must be directed at the weed and away from the crop. Glufosinate is a post-emergence herbicide applied at 0.35–1.7 kg AI ha^{-1}, used in much the same way as bilanafos, except with glufosinate-resistant crops, with which it can sprayed directly on the crop. No weed resistance has evolved to either bilanafos or glufosinate.

Bilanafos and glufosinate are relatively non-toxic to mammals and other non-target organisms.[47,48] They have very little activity in soil, mainly owing to rapid microbial degradation. They are considered to be low environmental impact herbicides.

2.3 Insecticides and acaricides

2.3.1 The avermectins

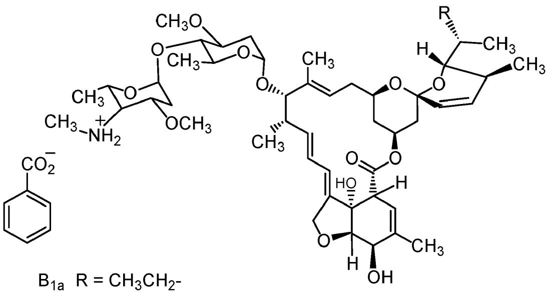
Abamectin (BSI, E-ISO, ANSI) (Fig. 3) is an insecticide and acaricide that is the fermentation product from the soil-dwelling actinomycete *Streptomyces avermitilis* M.S.T.D. It was isolated as part of a programme targeted at identifying new, biologically active secondary metabolites, being discovered in an *in vivo* screen when microbial fermentation broths were tested



(i) R = $-CH_2CH_3$ (avermectin B_{1a})

(ii) R = $-CH_3$ (avermectin B_{1b})

Abamectin: (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5'*S*,6*S*,6'*R*,8*R*,12*S*,13*S*,20*R*,21*R*,24*S*)-6'-[(*S*)-*sec*-butyl]-21,24-dihydroxy-5',11,13,22-tetramethyl-2-oxo-3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-(5',6'-dihydro-2'*H*-pyran)-12-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside



B_{1a} R = CH_3CH_2-

B_{1b} R = CH_3-

Emamectin benzoate: (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5'*S*,6*S*,6'*R*,8*R*,12*S*,13*S*,20*R*,21*R*,24*S*)-6'-[(*S*)-*sec*-butyl]-21,24-dihydroxy-5',11,13,22-tetramethyl-2-oxo-3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-(5',6'-dihydro-2'*H*-pyran)-12-yl 2,6-dideoxy-3-*O*-methyl-4-*O*-(2,4,6-trideoxy-3-*O*-methyl-4-methylamino-α-L-*lyxo*-hexopyranosyl)-α-L-*arabino*-hexopyranoside (90%) and (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5'*S*,6*S*,6'*R*,8*R*,12*S*,13*S*,20*R*,21*R*,24*S*)-21,24-dihydroxy-6'-isopropyl-5',11,13,22-tetramethyl-2-oxo-3,7,19-trioxatetracyclo[15.6.1.$1^{4,8}$.$0^{20,24}$]pentacosa-10,14,16,22-tetraene-6-spiro-2'-(5',6'-dihydro-2'*H*-pyran)-12-yl 2,6-dideoxy-3-*O*-methyl-4-*O*-(2,4,6-trideoxy-3-*O*-methyl-4-methylamino-α-L-*lyxo*-hexopyranosyl)-α-L-*arabino*-hexopyranoside (10%)

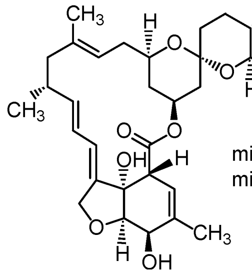
Figure 3. Bacteria-derived insecticides.

in mice against the nematode *Nematospiroides dubius* Baylis in a dual mice–nematode system.[49,50] The product is a mixture of two avermectins, avermectin B_{1a} and avermectin B_{1b}, and was introduced as an insecticide/acaricide by Merck Sharp and Dohme Agvet, but it is now owned by Syngenta.

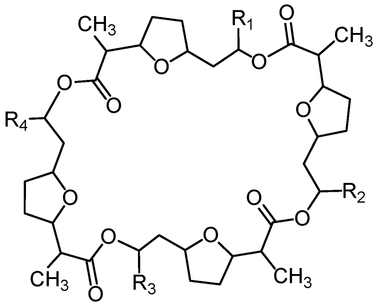
It has the approved common names abamectin (BSI, draft E-ISO, ANSI) and abamectine [(*f*) draft F-ISO], but it is also known as avermectin B1. The CAS registry numbers are *[71 751-41-2]* for abamectin, *[65 195-55-3]* for avermectin B_{1a} and *[65 195-56-4]* for avermectin B_{1b}.

Abamectin is recommended for use on ornamentals, cotton, citrus fruit, pome fruit, nut crops, vegetables, potatoes and many other crops to control the motile stages of a wide range of mites, leafminers, suckers, beetles and other insects, and it is also used for control of fire ants (*Solenopsis* spp.).

The target for abamectin is the γ-aminobutyric acid (GABA) receptor in the peripheral nervous system.[51] The compound stimulates the release of GABA from nerve endings and enhances the binding of GABA to receptor sites on the post-synaptic membrane of inhibitory motor neurons of nematodes and on the post-junction membrane of muscle cells of insects and other arthropods. This enhanced GABA binding 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.[52] It is an insecticide and acaricide with contact and stomach action,



Milbemycin: (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5'*S*,6*R*,6'*R*,8*R*,13*R*,20*R*,21*R*,24*S*)-21,24-dihydroxy-5',6',11,13,22-pentamethyl-3,7,19-trioxatetracyclo[15.6.1.1^{4,8}.0^{20,24}]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one and (10*E*,14*E*,16*E*,22*Z*)-(1*R*,4*S*,5'*S*,6*R*,6'*R*,8*R*,13*R*,20*R*,21*R*,24*S*)-6'-ethyl-21,24-dihydroxy-5',11,13,22-tetramethyl-3,7,19-trioxatetracyclo[15.6.1.1^{4,8}.0^{20,24}]pentacosa-10,14,16,22-tetraene-6-spiro-2'-tetrahydropyran-2-one



dinactin: R_1, R_3 = CH_3- ; R_2, R_4 = CH_3CH_2-
trinactin: R_1 = CH_3- ; R_2, R_3, R_4 = CH_3CH_2-
tetranactin: R_1, R_2, R_3, R_4 = CH_3CH_2-

Dinactin:
[1*R*(1*R**,2*R**,5*R**,7*R**,10*S**,11*S**,14*S**,16*S**,19*R**,20*R**,23*R**,25*R**,28*S**,29*S**,32*S**,34*S**)]-5,23-diethyl-2,11,14,20,29,32-hexamethyl-4,13,22,31,37,38,39,40-octaoxapentacyclo[32.2.1.1^{7,10}.1^{16,19}.1^{25,28}]tetracontane-3,12,21,30-tetrone

Trinactin:
[1*R*(1*R**,2*R**,5*R**,7*R**,10*S**,11*S**,14*S**,16*S**,19*R**,20*R**,23*R**,25*R**,28*S**,29*S**,32*S**,34*S**)]-5,14,23-triethyl-2,11,20,29,32-pentamethyl-4,13,22,31,37,38,39,40-octaoxapentacyclo[32.2.1.1^{7,10}.1^{16,19}.1^{25,28}]tetracontane-3,12,21,30-tetrone

Tetranactin:
[1*R*(1*R**,2*R**,5*R**,7*R**,10*S**,11*S**,14*S**,16*S**,19*R**,20*R**,23*R**,25*R**,28*S**,29*S**,32*S**,34*S**)]-5,14,23,32-tetraethyl-2,11,20,29-tetramethyl-4,13,22,31,37,38,39,40-octaoxapentacyclo[32.2.1.1^{7,10}.1^{16,19}.1^{25,28}]tetracontane-3,12,21,30-tetrone

Figure 3. Continued.

with only limited plant systemic activity but some translaminar movement.

It is sold as an EC formulation and as a ready-for-use bait (RB) under a wide variety of trade names including Agrimec, Dynamec, Vertimec, Affirm (for fire ant control), Agri-Mek (for use in citrus), Avid (for use in ornamentals), Clinch and Zephyr (for use in cotton) from Syngenta, Abacide from Mauget, Gilmectin from Gilmore, Satin from Sanonda, Abamex and Vapcomic from Vapco, Biok from Cequisa, Romectin from Rotam, Timectin from Tide, Vibamec from Vipesco, Agromec from Chemvet, Apache and Crater from AFRASA, Belpromec from Probelte, Vamectin 1.8 EC from IQV and Vivid from Florida Silvics. Abamectin is used at rates of 5.6–28 g AI ha^{-1} for mite control and 11–22 g AI ha^{-1} for control of leafminers, and the effectiveness of the product is increased significantly by the addition of paraffinic oils to the spray tank. Abamectin has secured a good market share because of its high level of biological activity and broad spectrum.

Although relatively high in its mammalian toxicity, its high biological effect on insects and mites means

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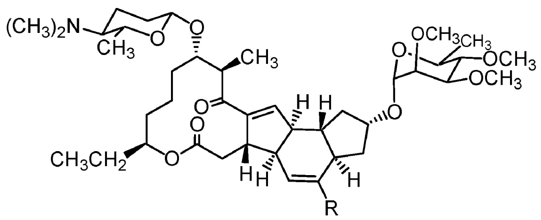

spinosyn A, R = H-

spinosyn D, R = CH_3-

Spinosyn A: (2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-8-oxacyclododeca[*b*]*as*-indacene-7,15-dione

Spinosyn D: (2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*S*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-8-oxacyclododeca[*b*]*as*-indacene-7,15-dione

Figure 3. Continued.

that only very low rates are used, thereby retaining a wide margin of safety between target insects and non-target species and humans.[53–55]

Abamectin binds tightly to soil, with rapid degradation by soil microorganisms, and consequently there is no bioaccumulation.

Emamectin benzoate (BSI, E-ISO, ANSI) (Fig. 3) is an insecticide and acaricide that was synthesised from the naturally occurring insecticide/acaricide abamectin and, as such, is only included in this review for completeness.[56,57] It consists of two homologues, emamectin B_{1a} and emamectin B_{1b}, and was introduced by Merck Sharp and Dohme Agvet, but is now owned by Syngenta.

Chemically it is a 90:10 mixture of two isomers with the CAS registry number *[155 569-91-8]*, formerly *[137 512-74-4]* and *[179 607-18-2]*.

Emamectin benzoate is particularly effective against caterpillar pests (Lepidoptera), with suppressive activity against mites, leaf miners and thrips.[58] It is recommended for use in vegetables, maize (corn), tea, cotton, peanuts and soybeans, with another recommendation for injection into pine trees for control of pinewood nematodes [*Bursaphelenchus xylophilus* (Steiner & Buhrer) Nickle].[59]

The target for emamectin is the GABA receptor in the peripheral nervous system (see under abamectin above).[51] It is an insecticide with contact and stomach action, with limited plant systemic activity, but exhibits translaminar movement. Emamectin benzoate irreversibly paralyses treated lepidopteran insects, preventing subsequent crop damage. The lepidopteran stops feeding within hours of ingestion and dies 2–4 days after treatment.

It is sold as WG and EC formulations under the trade names Proclaim, Affirm, Shot-One, Arise and Denim, all produced by Syngenta. It is used at rates between 5 and 25 g AI ha^{-1}, and the effectiveness of the product is increased significantly by the addition of paraffinic oils to the spray tank.

Emamectin benzoate has a lower mammalian toxicity than abamectin, but it is very active against beneficial insects such as honey bees and as such should not be sprayed during flowering.[51]

2.3.2 *Milbemycin*

Milbemycin (BSI, E-ISO) (Fig. 3) (also known as milbemectin) is an insecticide and acaricide that is the fermentation product from the soil-dwelling actinomycete *S. hygroscopicus* subsp. *aureolacrimosus*.[60] It was introduced by Sankyo Agro. It is a mixture of milbemycin A_3 and milbemycin A_4 in the ratio 3:7. The CAS registry numbers are *[51 596-10-2]* for milbemycin A_3 and *[51 596-11-3]* for milbemycin A_4.

Milbemycin is used for the control of citrus red mites [*Panonychus citri* (McGregor)], pink citrus rust mites [*Aculops pelekassi* (Keifer)], Kanzawa spider mites (*Tetranychus kanzawai* Kishida) and other spider mites, and is also recommended for control of leaf miners in citrus fruit, tea, aubergines and protected ornamentals.[61]

Milbemycin stimulates the release of GABA from nerve endings and enhances the binding of this to receptor sites on the post-synaptic membrane of inhibitory motor neurons of mites and other arthropods. This enhanced GABA binding 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.[54] It is an acaricide with contact and stomach action, with limited plant systemic activity, but it does exhibit translaminar movement.

Milbemycin is sold as EC and WP formulations under the trade names Milbeknock, Koromite and Matsuguard (for pinewood nematode control) by Sankyo Agro and Ultiflora and Mesa by both Gowan and Sankyo Agro. It is used at 5.6–28 g AI ha^{-1} for mite control, and its effectiveness is increased significantly by the addition of paraffinic oils to the spray tank. It has never achieved a significant market share. The semi-synthetic analogue milbemycin oxime has found uses for the treatment of heartworm and various nematodes in animals such as dogs. It is sold under the trade names Inceptor and Sentinel.

Milbemycin has a moderate oral mammalian toxicity but is much less toxic via the dermal route. It does not persist in the environment and is considered to be relatively non-toxic to non-target organisms, although some beneficial insects are susceptible.

2.3.3 Polynactins

Polynactins (JMAF) (Fig. 3) are secondary metabolites from the actinomycete *S. aureus* Waksman & Henrici isolate S-3466 and are a mixture of tetranactin, trinactin and dinactin.[62]

The CAS registry numbers are *[20 261-85-2]* for dinactin, *[7561-71-9]* for trinactin and *[35 396-61-5]* for tetranactin.

Polynactins are used to control spider mites, such as carmine spider mite [*Tetranychus cinnabarinus* (Boisduval)], two-spotted mite [*T. urticae* (Koch)] and European red mite (*Panonychus ulmi* Koch) in orchard fruit trees.

The polynactins are very effective at controlling spider mites under wet conditions. The mode of action is thought to be through a leakage of basic cations (such as potassium ions) through the lipid layer of the membrane in the mitochondrion. Water is considered to be an essential component of this toxic effect by either assisting penetration or accelerating ion leakage.[63]

The products are sold in combination with other acaricides as EC formulations under the trade names Mitecidin (plus fenobucarb) and Mitedown (plus fenbutatin oxide) by Eikou Kasei, although their continued sale is under review.

The polynactins are not considered to be toxic to mammals and are relatively non-toxic to beneficial insects, although they do have a high toxicity to fish.

2.3.4 Spinosad

Spinosad (BSI, ISO, ANSI) (Fig. 3) is a secondary metabolite from the soil actinomycete *Saccharopolyspora spinosa* Mertz & Yoa. The parent strain was originally isolated from an abandoned rum still in the Caribbean by Elanco in 1982 and introduced commercially in 1997 by Dow AgroScience.[64]

Spinosad is a mixture of spinosyn A and spinosyn D, which have the CAS registry numbers *[168 316-95-8]* for spinosad, *[131 929-60-7]* for spinosyn A and *[131 929-63-0]* for spinosyn D.

Spinosad is recommended for the control of a very wide range of caterpillars, leaf miners, thrips and foliage-feeding beetles. Species controlled include caterpillars [*Ostrinia nubilalis* (Hübner), *Helicoverpa zea* Boddie, *Trichoplusia ni* (Hübner), *Plutella xylostella* (L.), *Spodoptera* spp., *Heliothis* spp., *Pieris rapae* (L.), *Keiferia lycopersicella* (Walsingham), *Lobesia botrana* (Denis & Schiffermüller), *Agrotis ipsilon* (Hufnagel) and *Parapediasia teterrella* (Zincken)], thrips such as *Frankliniella occidentalis* (Pergande) and *Thrips palmi* (Karny), flies, including *Liriomyza* spp. and *Ceratitis capitata* (L.), beetles [*Leptinotarsa decemlineata* (Say)], drywood termites [*Cryptotermes brevis* (Walker), *Incisitermes snyderi* (Light)], fire ants (*Solenopsis* spp.) and grasshoppers. It is also under development for control of chewing and sucking lice, e.g. *Linognathus vituli*, *Bovicola ovis* (Schrank) and *Solenopotes capillatus* Enderlein, and flies, e.g. *Haematobia irritans* (L.) and *Lucilia cuprina* (Wiedemann), and for control of nuisance flies, e.g. *Stomoxys calcitrans* (L.) and *Musca domestica* L. Spinosad may be used on row crops (including cotton), vegetables, fruit trees, turf, vines and ornamentals, and it is under development for use on livestock animals and in livestock premises.[65,66]

Spinosad effects on target insects are consistent with the activation of the nicotinic acetylcholine receptor, but at a different site than nicotine or the neonicotinoids. Spinosad also affects GABA receptors, but their role in the overall activity is unclear. There is currently no known cross-resistance to other insecticide classes. The mode of action causes rapid death of target phytophagous insects. Its moderate residual activity reduces the possibility of the onset of resistance, but it is strongly recommended that it be used within a strong, proactive resistance management strategy.[67]

Spinosad is sold as a water-based suspension concentrate (SC) formulation under the trade names Conserve, Entrust, Success, SpinTor, Tracer, GF-120, Justice, Laser, Naturalyte and Spinoace by Dow AgroScience. It is used at rates between 5 and 150 g AI ha^{-1}. Clearance for use in organic systems has increased the potential market for spinosad, and it continues to sell well in conventional and integrated farming systems. Dow AgroScience is developing new natural insecticides with similar chemistry to spinosad.

Spinosad has a very low mammalian toxicity and is considered to be practically non-toxic to birds but slightly to moderately toxic to fish. It is highly toxic to honey bees, with less than 1 mg/bee of technical material applied topically resulting in mortality. Once residues are dry, however, they are non-toxic. Spinosad is rapidly degraded on soil surfaces by photolysis and, below the soil surface, by soil microorganisms.[68]

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3 FUNGUS-DERIVED PRODUCTS

3.1 Fungicides and bactericides

The only product derived from fungi that is sold as a fungicide/bactericide is yeast extract hydrolysate, a byproduct of the fermentation of brewers yeast (*Saccharomyces cerevisiae* Meyer ex Hansen).[69] It is sold as an end-use product under the trade name KeyPlex 350 by Morse Enterprises, but its composition is not clearly defined and its inclusion here is for completeness only.

3.2 Herbicides

Although there are many highly potent phytotoxins derived from fungi,[7] none of these is sold as a herbicide.

3.3 Insecticides, acaricides and nematicides

3.3.1 *Myrothecium verrucaria*

Myrothecium verrucaria (Alb. & Schwein.) Ditmar isolate AARC-0255 is a fungus (anamorphic Hypocreales: previously classified as mitosporic fungus and Deuteromycetes: Moniliales) that occurs in soil. The commercial isolate was derived from a nematode in the USA by Abbott (the product is now owned by Valent BioSciences). It is included in this review on natural products because the dried mycelium is used as a nematicide, and there is no evidence that the biological effect is caused by the fungus rather than the compounds within that mycelium – this makes it a natural, if undefined, 'chemical'.

The product is effective against plant parasitic nematodes, including root-knot (*Meloidogyne* spp.), cyst (*Heterodera* spp.), sting (*Belonolaimus longicaudatus* Rau) and burrowing [*Radopholus similis* (Cobb) Thorne] nematodes, and it is used in turf, tobacco, grapes, citrus, brassicae and bananas.

The active ingredient is the mixture of substances that are in suspension and in solution when the fungus *M. verrucaria* is grown in the laboratory. To prepare the active ingredient as a dry powder, water is removed from the culture mixture and the fungus is killed by exposure to high temperatures. The pesticidal activity is apparently not due to a single identifiable component but requires the entire mixture.[70,71] Researchers do not know the mechanism of action, but it controls both adult and juvenile nematodes on contact and inhibits the hatching and development of eggs. It has been shown to inhibit motility and to modify behaviour, including host and mate finding. It is sold by Valent BioSciences as a dry powder formulation DiTera, as a dry flowable DiTera DF and as a liquid formulation DiTera ES. DiTera DF is listed by the US Organic Materials Review Institute (OMRI) for use in organic production.

The pesticide product is incorporated into the upper 1–2.5 cm of soil as a dry powder or as a ground spray. It can be applied at any time in the life cycle of the plant: before planting, during planting or after planting. DiTera is recommended for use in a wide range of agricultural and horticultural crops. The lack of good alternative nematode control agents has meant that DiTera is increasing its market share.

Toxicological studies indicate a very favourable acute and non-acute toxicological profile. There is no evidence of allergic reactions. *Myrothecium verrucaria* occurs widely in nature and is not expected to have any adverse effects on non-target organisms or on the environment. The only known risk to the environment from the use of products containing this active ingredient concerns possible toxicity to aquatic organisms, and consequently it is not recommended to use the pesticide in or near bodies of water. The living fungus causes plant disease, but the active ingredient does not contain living *M. verrucaria* and therefore cannot infect plants.

4 PLANT-DERIVED PRODUCTS

4.1 Fungicides and bactericides

4.1.1 *Cinnamaldehyde*

Cinnamaldehyde (Fig. 4) occurs as the major component of oil found in fresh seeds of cassia plants, *Cassia tora* L. (also known as *Cassia obtusifolia* L.), but it is usually synthesised for use in crop protection. It has the IUPAC chemical name 3-phenyl-2-propenal and the CAS registry number *[104-55-2]*. It is used in mushrooms, row crops, horticultural crops, turf and pine forests to control diseases such as dry bubble [*Verticillium fungicola* (Preuss) Hassebrauk], other *Verticillium*, *Rhizoctonia* and *Pythium* species, dollar spot (*Sclerotinia homeocarpa* Bennett) and pitch canker disease (*Fusarium moniliforme* var *subglutinans* Wollenw. & Reinking). It is used as an attractant for corn rootworm (*Diabrotica* spp.) and as a repellent for cats and dogs.

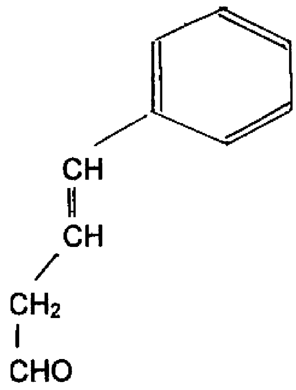
The mode of action of cinnamaldehyde is not understood. Its specificity to particular genera of plant pathogens suggests that it is more than a simple disruption of the fungal membranes. Its repellent and attractant properties are based on its strong odour.

Cinnamaldehyde is sold as a WP formulation under the trade names Vertigo by Monterey and Cinnacure by Proguard. It is applied as a preventive treatment, at the rate of 0.2–0.5% cinnamaldehyde. It is sprayed around areas to be protected from cat and dog invasions.[2]

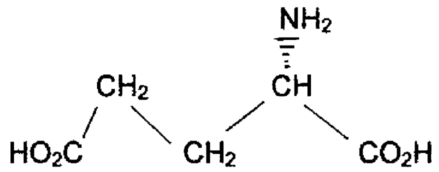
The products have low mammalian toxicity, although they can cause moderate eye and skin irritation. Cinnamaldehyde is not soluble in water and is degraded rapidly in the soil, and it is not expected to pose any hazard to non-target organisms or to the environment. It is not widely used in crop protection, but finds markets in home and garden use.

4.1.2 *L-Glutamic acid plus γ-aminobutyric acid*

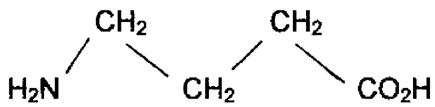
Auxien has registered the combination product containing L-glutamic acid and γ-aminobutyric acid (Fig. 4) as AuxiGro for use as a fungicide and plant growth regulator. The two active ingredients are found in virtually all living organisms and, in their pure form,



Cinnamaldehyde



L-Glutamic acid



γ-Aminobutyric acid

Figure 4. Plant-derived fungicides and bactericides.

are powders. They have the CAS registry numbers *[56-12-2]* for γ-aminobutyric acid and *[56-86-0]* for L-glutamic acid.

AuxiGro is used in certain fruits and vegetables, tree nuts, peanuts, grains, animal feed crops, lawn and turfgrasses and ornamentals as a growth enhancer that both increases yield and improves quality, as well as preventing powdery mildew on grapes and suppressing certain other crop diseases. AuxiGro has received US-EPA registration for use on snap beans, cucumbers, navy beans, pinto beans, grapes, bulb onions, peppers, strawberries, watermelons, celery, lettuce, peanuts, potatoes and tomatoes. It has an 'exemption from tolerance' for all crop applications.

One component of AuxiGro is γ-aminobutyric acid (GABA), a natural product found in bacteria, plants and all animals, including humans. The other active ingredient is the immediate precursor to GABA, L-glutamic acid, a naturally occurring amino acid found in all living organisms. L-Glutamic acid is one of the major amino acids in plant and animal proteins and is also involved in many physiological functions. Both active ingredients act as neurotransmitters in the brain. These naturally occurring products are neither fertilisers, pesticides nor conventional plant growth regulators, but form a new category for which the term 'plant metabolic primer' has been introduced to describe their biological function.[2,69]

AuxiGro is sold as a WP formulation containing 29.2% GABA and 36.5% L-glutamic acid by Auxein Corporation. It can be applied by spraying from the ground or the air, by drenching the soil or through certain irrigation systems. To prevent powdery mildew, the pesticide product must be applied before the disease develops.

No risks to human health are expected from the use of L-glutamic acid and GABA as pesticide active ingredients. Toxicity tests in animals and humans showed no adverse effects from either component. No risks to the environment are expected from the use of these active ingredients, because they occur naturally and do not persist in the environment. They are not toxic to mammals or other organisms tested and they are not likely to be toxic to plants, given that they enhance growth of many kinds of plant.

4.1.3 Jojoba oil

Jojoba oil is derived from jojoba seeds (*Simmondsia californica* Nutt. and *S. chinensis* Link.). It consists of straight-chain wax esters, 36–46 carbon atoms in length, each consisting of an ester-linked fatty acid and a fatty alcohol. Each molecule has two points of *cis*-unsaturation, both located at the ninth carbon atom from either end of the molecule. It has been recognised as effective against whitefly and was first registered in the USA in 1994. In 1998, jojoba wax was found to control powdery mildew on a number of plant species.

IJO Products markets three formulations – Detur is used for whitefly [*Bemisia* spp. and *Trialeurodes vaporariorum* (Westwood)] control in melons, vegetables, cotton, ornamentals and other crops, and E-Rase and Eco E-Rase are recommended for powdery mildew control in ornamentals, grapes, vegetables and many other crops. Soil Technologies sells Permatrol for use in grapes and in ornamentals grown in the field, in glasshouses, in shadehouses and in nurseries.

The mode of action and the reason for jojoba oil specificity are not totally understood. Activity against whitefly eggs and immature life stages is a result of suffocation. Activity against adults is by repellency. Against powdery mildew, fungal spores and mycelium are killed by blocking access to oxygen.[2,69]

Although the chemical composition of jojoba oil is known, the compounds required for the activity of the oil as a fungicide are unknown. Jojoba oil is sold as a 97.5% jojoba oil formulation and is applied as a foliar spray, ensuring good coverage but avoiding run-off.

Jojoba wax derived from jojoba oil is a food additive, and jojoba oil is used as a skin oil. No harmful health effects to humans are expected from the use of jojoba oil in crop protection, and adverse effects to the environment or to organisms other than insects are not anticipated because of the low toxicity of jojoba oil and its rapid decomposition in the environment.

4.1.4 Laminarine

Laminarine (sometimes spelt laminarin), a storage polysaccharide of the marine brown alga, *Laminaria digitata* (Hudson), is a hydrophilic β-1,3-glucan with occasional β-1,6-linked branches. It has the CAS registry number *[9008-22-4]* and was developed following the observation that farmers in Northern France spread seaweed onto their fields which resulted in improved plant vigour and reduced incidence of fungal disease. In 1994, CNRS and Goëmar filed an international patent on the use of laminarine as a means of plant protection, completed field trials and sought a registration in France in 1998 which was granted in 2002. This compound is recommended for use against fungal pathogens of cereals, particularly septoria and powdery mildews.

Laminarine has no antifungal activity in its own right, but it stimulates the plant's natural defence mechanism, rendering it much less susceptible to attack; it acts as a systemic acquired resistance (SAR) inducer. It is recommended for use in cereals, particularly wheat.

Laminarine is sold as Iodus 40 by Goëmar as a liquid concentrate containing $40\,g\,AI\,L^{-1}$. The end-use product may be applied as a foliar spray with conventional ground or aerial spray equipment. It is not essential to give complete crop cover, but applications should be made before foliar diseases become established.[2]

Laminarine is considered to be non-toxic to mammals and is considered unlikely to have any adverse effects on non-target organisms or on the environment.

4.1.5 Milsana

Milsana is the partially refined extract of the giant knotweed plant [*Reynoutria sachalinensis* (Fr. Schm.) Nakai] and is also known as REYSA and *Reynoutria sachalinensis* extract. It was originally developed and sold by BASF AG in Europe, but is now under development by KHH BioSci Inc. for use in the Americas, Asia and Oceania.[72]

The technical-grade active ingredient consists entirely of the dried and ground plant material. The extract is recommended for use against a wide range of fungal pathogens, including *Botrytis* spp. and powdery mildews in ornamental and glasshouse crops, and in vegetable and fruit crops. Activity against some bacterial diseases, such as *Xanthomonas* spp., is also claimed. It is suggested that the high level of phenolics within treated plants also gives some protection against attack by phytophagous insects.

The extract, applied to growing plants at the onset of disease, prevents disease development by raising the plant's natural defence system. When applied to ornamental, vegetable and fruit crops, milsana will induce increased amounts of naturally occurring phenolic substances in the treated plants. These phenolics act as phytoalexins and have been shown to prevent the attack of several commercially important plant diseases, including powdery mildew and grey mould in ornamental plants, such as roses, and in vegetable and fruit crops, such as cucumbers, peppers and grapes.[73,74]

The end-product is a 5% ethanolic extract suspended in calcium nitrate solution sold by KHH BioScience under the trade name Milsana. It should be applied at 0.5% v/v in 500–1000L water ha^{-1}, sprayed at 7–10 day intervals with the addition of 0.02% v/v of an anionic wetting agent to the foliage at the four- to six-leaf stage of crops to be protected. Treated plants will also be darker green and senescence will be delayed. A second treatment may be applied after 14–21 days. The product has been shown to offer some protection to a variety of crops, but when sold in Germany it failed to secure a significant share of the market. It is expected that its clearance for use in organic farming will increase sales.

Milsana was commercialised in Germany for over 12 years, with no reports of any adverse effects. It is considered to be of low mammalian toxicity and is not expected to have any adverse effects on non-target organisms or on the environment.

4.1.6 Pink plume poppy extract

The extract of the pink plume poppy (*Macleaya cordata* R. Br.) has been registered for use as a fungicide under the trade name Qwel by Camas. *Macleaya cordata* extract contains several alkaloids, including sanguinarine, chelerythrine, protopine and allocryptopine, but Qwel contains mainly a mixture of sanguinarine chloride and chelerythrine chloride. This mixture has the CAS registry number *[112 025-60-2]*.

The target pathogens are those causing foliar fungal diseases, such as powdery mildew, alternaria leaf spot and septoria leaf spot in ornamental protected crops.

The mode of action has not been confirmed, but it is thought likely that, when applied to crops, Qwel induces increased amounts of naturally occurring phenolic substances in the treated plants. These phenolics act as phytoalexins, and, in this way, Qwel induces SAR. It is sold as a 1.5% aqueous extract.[2,69] Its approval for use in organic farming is seen as a means of increasing sales.

It is considered to be non-toxic to mammals and to non-target organisms and to be without adverse effects on the environment.

4.2 Herbicides

4.2.1 Acetic acid

Acetic acid (CH_3COOH, CAS registry number *[64-19-7]*) (commonly called vinegar as a dilute, aqueous solution) is a ubiquitous metabolite of most organisms. It is generally produced commercially by acetous fermentation of ethyl alcohol (made from grain). It is sold as horticultural vinegar in diluted aqueous solutions of up to 20% acetic acid for non-selective weed management. In some weed management products, acetic acid is blended with other plant-derived compounds or mixtures of compounds, such as clove oil (see below) and citric acid.

It is used for non-cropland areas, such as railway rights-of-way, golf courses, open space, driveways and industrial sites. It will burn off the tops of weeds, but it will not control the root system responsible for regeneration of plants. It is typically more effective against broadleaf than grassy weeds.[75,76] An acetic acid concentration from 10 to 20% controls most small weeds. 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.

Concentrations of acetic acid greater than 5% may be hazardous and should be handled with appropriate precautions.

4.2.2 Clove oil

Clove oil (CAS registry number *[8000-34-8]*) is produced by steam distillation of leaves of the clove (*Eugenia caryophyllus* Spreng) plant. Clove oil is a mixture of several predominantly terpenoid compounds. It has both insecticidal (see Section 4.3.1) and herbicidal activities. Eugenol (CAS registry number *[97-53-0]*) is the principal component of clove oil, and it is highly phytotoxic (Duke SO and Cantrell C, unpublished data). In fact, at least one product lists clove oil as eugenol. It is sold as a clove oil EC preparation (50% clove oil – Matran EC produced by EcoSmart) or in mixtures with acetic acid (12% clove oil in Burnout II Concentrate produced by St Gabriel Laboratories). The final spray solutions are recommended to be diluted to 2.5–4% clove oil. One preparation for poison ivy (*Rhus radicans* L.) control is applied at 12% clove oil (Poison Ivy Defoliant, St Gabriel Laboratories) formulated with 8% sodium lauryl sulfate.

Clove oil is a contact, non-selective foliar herbicide that will only control above-ground, green vegetation. It does not translocate. It causes rapid loss of cellular membrane integrity.

Clove oil has low oral and dermal toxicity and has relatively little potential environmental effects.

4.2.3 Fatty acids

The potential use of fatty acids as herbicides has been known for many years.[77,78] Several blends of fatty acid salts (sodium or potassium) that are found on both plants and animals are marketed as non-selective herbicides. For example, Naturell WK Herbicide is an effective total, non-residual herbicide, and DeMoss and Naturell WK Mosskiller control moss in lawns and moss and liverworts on fences, roofs and glasshouses. The exact constituents of most of these products are seldom provided. For example, the MSDS data sheet for DeMoss simply lists the active ingredients as 40% potassium salts of fatty acids. Oleic acid (Fig. 5) is usually a major component of these mixtures. Oleic acid is also a major constituent of neem oil (q.v. Section 4.3.2 on azadirachtin).

$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2M$

M = H, Na or K

Oleic acid (and salts)

$CH_3(CH_2)_7CO_2H$

Pelargonic acid

$CH_3CH_2CO_2(CH_2)_2C_6H_5$

2-Phenethyl propionate

Figure 5. Plant-derived herbicides.

Different fatty acids are effective as insecticides, fungicides, total herbicides or as moss killers. Trade names of some of these products are: M-Pede (a mixture of oleic and linoleic acids, as their potassium salts), Hinder (ammonium salts) (Amvac), Quik-RTU (ammoniated soap of fatty acids) (Monterey and Neudorff), Neo-Fat (Nufarm), Naturell, Naturell WK Mosskiller and Naturell WK Herbicide (Russell), Oleate (sodium salt) (Otsuka), Savona (potassium salts) (Koppert), Neu 1128 (potassium salts) (Neudorff) and Safer Moss and Algae Killer (40% potassium salts of fatty acids).

4.2.4 Pelargonic acid

Pelargonic acid (Fig. 5) is also known as nonoic acid or nonanoic acid (CAS registry number *[112-05-0]*). It occurs naturally in members of the family Geraniaceae. It is formulated as an EC containing 57% pelargonic acid with 13% emulsifiers and short-chain fatty acids and 30% paraffinic petroleum oil (Scythe I; Dow Agrosciences). Many of its properties are listed in detail in the Weed Science Society of America's Herbicide Handbook.[79] It is a contact, broad-spectrum herbicide that is not translocated, applied at rates of 10–95 kg AI ha^{-1} (9.5–84 lb $acre^{-1}$) for control of annual weeds, mosses and liverwort.[79–81] It disrupts plant cell membranes, causing rapid loss of cellular function.[82] When saturated fatty acids from C6 to C14 were compared, the C9 to C11 fatty acids were especially active, whereas the others were significantly less active.[83] C6 and C14 fatty acids had essentially no herbicidal activity. Pelargonic acid itself is considered a low toxicity and environmental impact herbicide.[77,79] It has no residual activity.

4.2.5 Maize gluten

Maize or corn gluten, a byproduct of the wet milling process of maize (*Zea mays* L.) grain, is being sold for pre-emergence weed management and fertilization. It is sold under many trade names in North America

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for organic weed management, with corn gluten meal varying from 60 to 99% between different products. It is applied to or worked into soil at a rate of 9 kg 100 m^{-2}. It has no activity on existing weeds, but inhibits germination and development of weeds from seeds. It is used in turf and garden with activity against most grass and broadleaf weed species in these settings. It apparently acts by hydrolysation of gluten proteins in the preparation by soil microbes to produce five different phytotoxic dipeptides[84] and a phytotoxic pentapeptide.[85] The hydrolysation process after application makes this a slow-release herbicide.

4.2.6 2-Phenethyl propionate

One product (EcoSmart HC or EcoExempt HC) for weed management is composed of equal amounts (21.4%) of clove oil and 2-phenethyl propionate (Fig. 5) (CAS registry number *[122-70-3]*); the latter is a component of peppermint oil that is used for flavouring food. It has been patented as a herbicide.[86] It is recommended that this product be diluted fourfold for spraying. Another brand (Bioorganic) is sold ready to be sprayed as 5% clove oil, 5% 2-phenethyl propionate, 4% sesame oil and 0.5% sodium lauryl sulfate. Its use recommendations are the same as for clove oil or eugenol (see above). This compound is thought to be very safe to the environment and to human health, as its active ingredients are food flavourings.

4.2.7 Pine oil

A 9.7–11.7% aqueous emulsion of pine (*Pinus* spp.) oil (CAS registry number *[8002-09-03]*) composed of terpene alcohols and saponified fatty acids is sold for weed control under the trade name of Interceptor by Certified Organics Ltd, Auckland, New Zealand. It is sprayed at a 10–20% dilution of the commercial product, with 4–25 L AI ha^{-1}, depending on the weed situation. It is a non-selective, contact herbicide that is used in the same way as products with similar activity. In some studies it has provided good weed control,[87] and in others it has not performed as well as some other natural product-based herbicides.[75] It is considered largely non-toxic to humans and the environment, but may have minor effects on aquatic organisms. It breaks down almost completely within 3 days of application. It is a fast-acting, non-selective contact herbicide that is not translocated.

4.3 Insecticides and acaricides

4.3.1 4-Allyl-2-methoxyphenol (eugenol)

There is no ISO common name for 4-allyl-2-methoxyphenol (Fig. 6); the name eugenol has been used in the literature but has no official status. It is found in a wide range of plants including laurel (*Laurus* species) and in clove oil (see Section 4.2.2). Clove oil is predominantly composed of 4-allyl-2-methoxyphenol, but also contains a small amount of acetyl 4-allyl-2-methoxyphenol.[69] 4-Allyl-2-methoxyphenol has the CAS registry number *[97-53-0]*, while clove oil is *[8000-34-8]*.

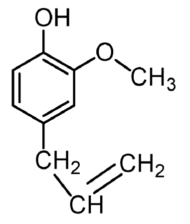
It is recommended for use against a wide range of insects including aphids, armyworms, beetles, cutworms, grasshoppers, loopers, mites and weevils in fruit and vegetable crops. 4-Allyl-2-methoxyphenol is a strong deterrent for most insect species, although in a few cases it can be an attractant. At high concentrations it is also an effective (organic farming approved), total, post-emergence herbicide. It is sold by a large number of different suppliers under many different trade names and is targeted at the home garden market. Typical products include Bag-a-Bug Japanese Beetle Trap and Japanese Beetle Combo Bait from Spectrum; Bioganic Flying Insect Killer (6% 4-allyl-2-methoxyphenol and 1% sesame oil), Bioganic Lawn and Garden Spray (0.45% 4-allyl-2-methoxyphenol plus 0.45% thyme oil plus 0.45% sesame oil) and Bioganic Dust (3.5% 4-allyl-2-methoxyphenol plus 1.5% phenethyl propionate) from Bioganic and Biocontrol Network; Ecozap Wasp and Hornet Insecticide, Ecozap Crawling and Flying Insecticide and Bioganic Weed and Grass Killer (2% 4-allyl-2-methoxyphenol plus 2% thyme oil plus 1% sodium lauryl sulfate plus 10% acetic acid) from Bioganic; EcoExempt HC (21.4% 4-allyl-2-methoxyphenol plus 21.4% 2-phenethyl propionate) and Matran (45.6% clove oil) from EcoSmart; Ecopco D Dust Insecticide, Ecopco AC Contact Insecticide and Ecopco Jet Wasp/Hornet/Yellow Jacket Contact Insecticide from EcoSmart; Ecosafe from Arbico; Japanese Beetle Bait II and Trece Japanese Beetle Trap from Trece; Ringer Japanese Beetle Bait from Woodstream; Surefire Japanese Beetle Trap from Suterra; and Vizubon-D (methyl salt plus naled) from Vipesco. The products are applied, in moderate volume, to foliage when insect pressure is increasing. The main use of these products is in home and amateur gardening.

4-Allyl-2-methoxyphenol is an irritant and should be used with care. Being a naturally occurring plant-based phenolic, it is not expected to be hazardous to non-target organisms or to the environment.

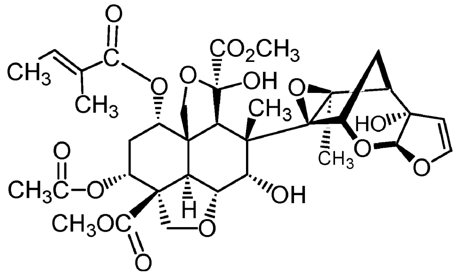
4.3.2 Azadirachtin/dihydroazadirachtin

Azadirachtin (Fig. 6) is extracted from the neem tree (*Azadirachta indica* A. Juss) which has long been known to resist insect attack. Subsequent investigation found that extracts, particularly of the seed, were insecticidal. The tree is an attractive broad-leaved evergreen which is thought to have originated in Burma. It is now grown in the more arid subtropical and tropical zones of Southeast Asia, Africa, the Americas, Australia and the South Pacific Islands.

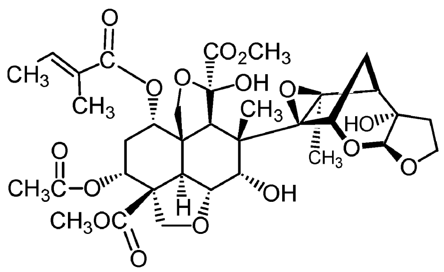
Azadirachtin[87–90] has the CAS registry number *[11 141-17-6]*. It is the principal insecticidal ingredient of neem seed extracts, although these extracts also contain a variety of limonoids, such as nimbolide, nimbin and salannin. Many products are also claimed to have fungicidal activity.



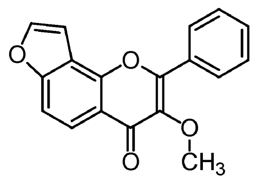
4-Allyl-2-methoxyphenol (eugenol)



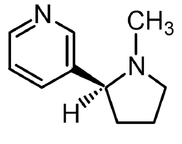
Azadirachtin: dimethyl (3*S*,3a*R*,4*S*,5*S*,5a*R*,5a^{1}*R*,7a*S*,8*R*,10*S*,10a*S*)-8-acetoxy-3,3a,4,5,5a,5a^{1},7a,8,9,10-decahydro-3,5-dihydroxy-4-{(1*S*,3*S*,7*S*,8*R*,9*S*,11*R*)-7-hydroxy-9-methyl-2,4,10-trioxatetracyclo[6.3.1.0^{3,7}.0^{9,11}]dodec-5-en-11-yl}-4-methyl-10[(*E*)-2-methylbut-2-enoyloxy]-1*H*,7*H*-naphtho[1,8a,8-*bc*:4,4a-*c'*]difuran-3,7a-dicarboxylate



Dihydroazadirachtin



Karanjin - 3-methoxy-2-phenyl-4*H*-furo[2,3-*H*]-1-benzopyran-4-one



Nicotine - (*S*)-3-(1-methylpyrrolidin-2-yl)pyridine

Figure 6. Plant-derived insecticides.

Azadirachtin is a potent deterrent to many different genera of insects, and it has been shown to be effective against whitefly, thrips, leaf miners, caterpillars, aphids, jassids, San José scale [*Diaspidiotus perniciosus* (Comstock)], beetles and mealybugs. Some formulations are recommended for use against balsam whiteflies [*Neodiprion abietis* (Harris)], yellow-headed spruce sawflies [*Pikonema alaskensis* (Rohwer)] and pine false webworms [*Acantholyda erythrocephala* (L.)]. Effects against phytopathogenic fungi, such

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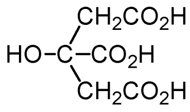


Citric acid

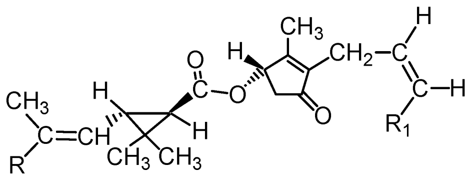
HCOOH

Formic acid

$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2M$

M = H, Na or K

Oleic acid (salts)



R = $-CH_3$ (chrysanthemates) or $-CO_2CH_3$ (pyrethrates)
R_1 = $-CH{=}CH_2$ (pyrethrin) or $-CH_3$ (cinerin) or $-CH_2CH_3$ (jasmolin)

Pyrethrin I - (*Z*)-(*S*)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; or (*Z*)-(*S*)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl (+)-*trans*-chrysanthemate

Cinerin I - (*Z*)-(*S*)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; or (*Z*)-(*S*)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (+)-*trans*-chrysanthemate

Jasmolin I - (*Z*)-(*S*)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (1*R*)-*trans*-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylate; or (*Z*)-(*S*)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (+)-*trans*-chrysanthemate

Pyrethrin II - (*Z*)-(*S*)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl (*E*)-(1*R*)-*trans*-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; or (*Z*)-(*S*)-2-methyl-4-oxo-3-(penta-2,4-dienyl)cyclopent-2-enyl pyrethrate

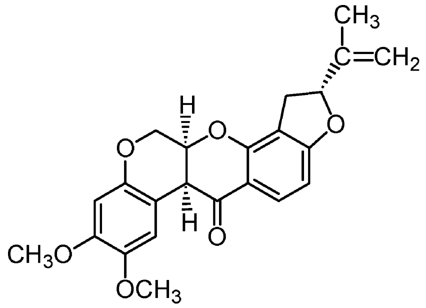
Cinerin II - (*Z*)-(*S*)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl (*E*)-(1*R*)-*trans*-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; or (*Z*)-(*S*)-3-(but-2-enyl)-2-methyl-4-oxocyclopent-2-enyl pyrethrate

Jasmolin II - (*Z*)-(*S*)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl (*E*)-(1*R*)-*trans*-3-(2-methoxycarbonylprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate; or (*Z*)-(*S*)-2-methyl-4-oxo-3-(pent-2-enyl)cyclopent-2-enyl pyrethrate

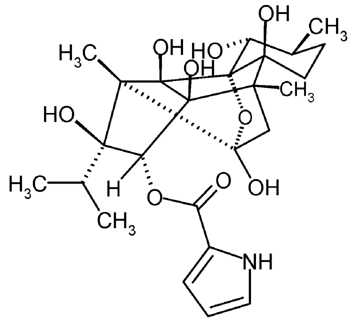
Figure 6. Continued.

as powdery mildews, are also claimed by some manufacturers. Products containing azadirachtin can be used in a wide range of crops, including vegetables (such as tomatoes, cabbage and potatoes), cotton, tea, tobacco, coffee, protected crops and ornamentals and in forestry.

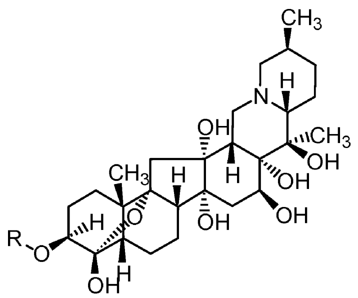
Azadirachtin has several effects on phytophagous insects and is thought to disrupt insect moulting by antagonising the effects of ecdysteroids. This leads to morphological defects in insects exposed to sprayed crops, and, in some cases, the larval period is extended. The ecdysis inhibition also leads to effects on vitellogenesis, leading to the reabsorption of vitellarium and oviducts, and this effect is independent of feeding inhibition, which is another observed effect of the compound.[91,92] The antifeedant/repellent effects are dramatic, with many insects avoiding treated crops, although other chemicals in the seed extract, such as salannin, have been shown to be responsible for these effects. The fungicidal and miticidal properties of the hydrophobic extract derive from physical smothering and desiccation. Its mode



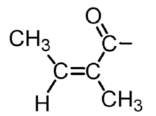
Rotenone - (2*R*,6a*S*,12a*S*)-1,2,6,6a,12,12a-hexahydro-2-isopropenyl-8,9-dimethoxychromeno[3,4-*b*]furo[2,3-*h*]chromen-6-one



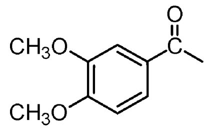
Ryanodine - (3S,4R,4aR,6S,6aS,7S,8R,8aS,8bR,9S,9aS)-dodecahydro-4,6,7,8a,8b,9a-hexahydroxy-3,6a,9-trimethyl-7-(1-methylethyl)-6,9-methanobenzo[1,2]pentaleno[1,6-bc]furan-8-yl 1H-pyrrole-2-carboxylate



cevadine (i) R =



veratridine (ii) R =



Cevadine - 4β,12,14,16β,17,20-hexahydroxy-4a,9-epoxycevan-3β-yl [(*Z*)-2-methylbut-2-enoate]

Veratridine - 4β,12,14,16β,17,20-hexahydroxy-4a,9-epoxycevan-3β-yl 3,4-dimethoxybenzoate

Figure 6. Continued.

of action means that azadirachtin is slow to control insects, particularly when populations are high.

Azadirachtin is sold by a large number of different companies as an EC under a wide range of trade names. These include Azatin, Align, Bio-neem, Bollwhip, Neem, Neemazad, Neemix, Neemgard, Neem Oil 70% (hydrophobic extract of neem oil), Niblecidine, Superneem 4.5-B, Triact, Trilogy (hydrophobic extract of neem oil) and Turplex from Certis; Amazin 3% EC from Amvac and Fortune; Anti-Pest-O from Holy Terra; Amvac Aza 3% EC, Ecozin 3% EC and Ornazin 3% EC from Amvac; Fortune Aza and Fortune Biotech from Fortune; Neem Suraksha, Proneem, Neem Wave and Aza Technical from Karapur Agro; Neemazal T/S 1.2% EC from EID Parry; NeemAzad from EID Parry and Andermatt; Neememulsion from Cyclo; Kayneem (neem oil) from Krishi Rasayan; Neemitaf (300 $mg\,L^{-1}$ azadirachtin) and Neemitox (1500 $mg\,L^{-1}$ azadirachtin) from Rallis; Nimbecidine from Stanes and PBT International; Blockade from RPG; Neemolin (seed extract) from Rallis; Neem Cake and Agroneem from Agro Logistics; AZA-Direct from Gowan; EI-783, EI-791 and Azatrol EC from

PBI/Gordon; Jawan from JB Chemicals; Neemactin from Biostadt; Trineem from Tagros; BioNeem from Biocontrol Network and Safer; NeemPlus Liquid from Biocontrol Network; K+ Neem (plus insecticidal soap) from Organica; Margosom from Agri Life and SOM Phytopharma; AquaNeem from SOM Phytopharma; and Vineem from Vipesco.

It is applied at rates of 100–500 g AI ha^{-1} (0.15–0.65 oz AI $acre^{-1}$), and it has been shown that frequent applications are more effective than single sprays.

Azadirachtin is the principal insecticidal ingredient of neem (*A. indica*) seed extracts. Neem emulsion is made from material containing 25% w/w azadirachtin, 30–50% other limonoids, 25% fatty acids and 7% glycerol esters. In all cases there are other components in each formulation, but the minimum claimed concentration of azadirachtin is guaranteed by the manufacturer. Azadirachtin-based products are widely used in India and are increasingly popular in North America where they have found a place for garden use and in organic growing.

There are no known incompatibilities with other crop protection agents, although, when neem was mixed with fenvalerate, its efficacy against the bollworm was reduced. Some neem formulations based on neem oil have resulted in severe phytotoxicity in rice. Azadirachtin is considered to be non-toxic to mammals and is not expected to have any adverse effects on non-target organisms or the environment.[93–95]

Dihydroazadirachtin (DAZA) (Fig. 6) is a reduced (hydrogenated) form of the naturally occurring azadirachtin obtained from the seed kernels of the neem tree, *A. indica*. It is effective against a wide range of insect pests and is recommended for use on horticultural and ornamental plants, trees and shrubs and on turfgrass, fibre crops, forage and fodder crops and other agricultural crops.

Dihydroazadirachtin is structurally similar to azadirachtin, with the CAS registry number *[108 189-58-8]*. The two compounds are functionally identical in their antipupation properties. DAZA has both antifeedant and insect growth regulator properties. It is registered as an end-use product for indoor and outdoor use under the trade name DAZA by SOM Phytopharma. The recommendation for use is foliar application by ground or aerial equipment at a rate of 50 g AI ha^{-1} (0.08 oz AI $acre^{-1}$), no more than 7 times a season on plants that are potted, grown in soil or soil-less mixtures grown hydroponically, including bedding plants, flowers, potted plants and foliage plants, ornamentals, trees and shrubs, turfgrass, fibre crops, forage and fodder crops and other agricultural crops.[2] Products based on dihydroazadirachtin are not widely used outside the Indian subcontinent, although it is registered as a technical powder and an end-use product for indoor and outdoor use in the USA.

Dihydroazadirachtin is of low mammalian toxicity, and risk to the environment is not expected because, under approved use conditions, it is not persistent, is relatively short-lived in the environment (of the order of days) and is metabolised by ubiquitous microorganisms in the soil and aquatic environments.[2]

4.3.3 *Karanjin*

Karanjin (Fig. 6) is extracted from pongam or Indian beech *Derris indica* (Lam.) Bennet [synonym *Pongamia pinnata* (L.) Pierre]. Karanjin has the CAS registry number *[521-88-0]*.[96] It is used for control of mites, scales, chewing and sucking insect pests and some fungal diseases.[2,97] It is a potent deterrent to many different genera of insects and mites and is effective against whitefly, thrips, leaf miners, caterpillars, aphids, jassids, San José scale, beetles and mealybugs in a wide range of crops, including vegetables (such as tomatoes, cabbage and potatoes), cotton, tea, tobacco, coffee, protected crops and ornamentals.

Karanjin has a dramatic antifeedant/repellent effect, with many insects avoiding treated crops. It suppresses the effects of ecdysteroids and thereby acts as an insect growth regulator (IGR) and antifeedant. There are claims that it inhibits cytochrome P450 in susceptible insects and mites. It is sold as a 20 g L^{-1} EC under the trade name Derisom by Agri Life and SOM Phytopharma. Karanjin has not achieved wide acceptance as an insecticide.

There is no evidence of allergic or other adverse effects on producers, formulators or users and it is not expected that karanjin-based products will have any adverse effects on non-target organisms or on the environment.

4.3.4 *Nicotine*

Nicotine (Fig. 6) (BSI, E-ISO, F-ISO, ESA, in lieu of a common name) is the main bioactive component of the tobacco plants *Nicotiana tabacum* L., *N. glauca* Graham and, particularly, the species *N. rustica* L.[98] It is also present in a number of other plants belonging to the families of Lycopodiaceae, Crassulaceae, Leguminosae, Chenopodiaceae and Compositae. The average nicotine content of the leaves of *N. tabacum* and *N. rustica* is 2–6% dry weight. Nicotine has the CAS registry numbers *[54-11-5]* for the (*S*)-isomer, *[22 083-74-5]* for the (*RS*)-isomers, *[75 202-10-7]* for unstated stereochemistry and *[65-30-5]* for the (*S*)-isomer of nicotine sulfate.

It is used for the control of a wide range of insects, including aphids, thrips and whitefly, on protected ornamentals and field-grown crops, including orchard fruit, vines, vegetables and ornamentals. It was once prepared from extracts of the tobacco plant but is now often obtained from waste of the tobacco industry, or it is synthesised. Its use is mainly confined to small-scale or glasshouse application. Nicotine is a non-systemic insecticide[99] that binds to the cholinergic acetylcholine nicotinic receptor in the nerve cells of insects, leading to a continuous firing of this neuroreceptor.[100,101] It is active predominantly through the vapour phase, but also has slight contact and stomach action. Nicotine has been used for many years as a fumigant for the control of many sucking insects. It can be used to give partial control of organophosphate- (OP) and pyrethroid-resistant whitefly. Nicotine has a rapid vapour action, with the laevorotatory isomer, (*S*)-nicotine, being 2–3 times more active than the other enantiomer.

Nicotine is sold as DP, SL and fumigant formulations under trade names such as Stalwart from United Phosphorus Ltd, No-Fid from Hortichem, XL-All Nicotine from Vitax, Nicotine 40% Shreds from Dow AgroSciences and Tobacco Dust from Bonide. It is applied as a foliar spray to cover the undersides of leaves, and repeated as necessary. Best results are achieved when the temperature is above 16 °C. If used as a fumigant, the temperature must be above 16 °C. The maximum number of treatments in protected annual crops is three.

Nicotine is very toxic to humans by inhalation and by skin contact.[102] The lethal oral dose for humans is stated to be 40–60 mg. It is toxic to birds, fish and other aquatic organisms, and is toxic to bees, but has a repellent effect. In the UK, nicotine is subject to regulation under the Poisons Act. The use of nicotine as a pesticide is banned in South Africa, severely restricted in Hungary and cancelled in Australia and New Zealand, as well as not being registered in numerous African, Asian and European countries. Nicotine 'tea' is cleared for use in organic systems.

4.3.5 *Phenethyl propionate*

Phenethyl propionate (Fig. 5) was discussed as a herbicide in section 4.2.6. It is also used as an insecticide/insect repellent and sold under a wide range of trade names in combination with other plant-derived natural products. Typical products are sold as lures, baits and ready-to-use formulations and include Hercon Japanese Beetle Food Lure (plus eugenol plus geraniol) from Aberdeen Road; Ecozap Wasp & Hornet Insecticide (plus eugenol) and Ecozap Crawling and Flying Insecticide (plus eugenol) from Biorganic; Ecopco Jet Wasp/Hornet/Yellow Jacket Contact Insecticide (plus eugenol), Ecopco Acu (plus eugenol), Bioganic Flying Insect Killer (plus eugenol) and Biorganic Granular Insecticide (plus thymol and eugenol) from Ecosmart; Raid Eo Ark (plus eugenol) from Johnson; Bag-a-Bug Japanese Beetle Trap (plus eugenol plus geraniol) and Japanese Beetle Combo Bait (plus eugenol plus geraniol) from Spectrum; Surefire Japanese Beetle Trap (plus eugenol plus geraniol) from Suterra; and Japanese Beetle Bait II (plus eugenol plus geraniol) and Trece Japanese Beetle Trap (plus eugenol plus geraniol) from Trece. The products must be applied liberally to areas to be protected from flying and biting insects, and lures and traps should be placed among the crops to be protected as soon as the target insects are sighted. The major use is in homes and gardens.

4.3.6 *Plant-derived oils*

A wide range of plant oils are being sold for insect and mite control. Among these are canola oil, an edible refined vegetable oil obtained from the seeds of two species of rape plants (*Brassica napus* L. and *B. campestris* L.) of the family Cruciferae (mustard family), jojoba oil, derived from jojoba seeds (see Section 4.1.3), oleoresin, derived from *Capsicum* spp., oil of anise, soybean oil and eucalyptus oil. More recently, hexa-hydroxyl, sold as a GR formulation containing 2.90% eugenol and 0.60% thyme oil as the active ingredients, and BugOil, made from the essential oils of three plant species, thyme (*Thymus vulgaris* L.), wintergreen (*Gaultheria procumbens* L.) and African marigold (*Tagetes erecta* L.), have been commercialised. Few of these oils have been fully characterised chemically, and their inclusion here is for completeness only. Some are also claimed to have fungicidal and herbicidal effects. Various claims are made for the mode of action, including insect repellency caused by altering the outer layer of the leaf surface, acting as an insect irritant and preventing gas exchange (suffocation) and water loss by covering the insect's body.[2,103] Fungicidal activity is thought to be due to prevention of gas exchange. These products are sold by a very large number of different companies under many different trade names. As they all occur naturally, it is generally claimed that their mammalian toxicity is low and that there are no adverse effects on non-target organisms or on the environment.

The potassium salts of plant oils (soft soaps) are also sold as insecticides under a wide range of trade names by many different manufacturers. They are recommended for use against aphids, caterpillars, earwigs, flea beetles, lace bugs, thrips, spider mites, mealybugs, leafhoppers, psyllids, sawfly larvae, scale crawlers, squash bugs and whitefly on a wide range of different crops, including bedding plants, flowers, foliage plants, fruits and nuts, herbs and spices, ornamentals, pot plants, trees and shrubs, vegetables and many others. Insecticidal soaps have not been chemically fully characterised and are contact insecticides, causing a breakdown of the target pest's cuticle, leading to dehydration and, ultimately, death. They cause the rapid knockdown of phytophagous insects, but, because they are broken down rapidly once sprayed, they will not prevent subsequent reinvasion. They are often used in conjunction with insect predators, being used to bring the populations down to manageable levels prior to release.

4.3.7 *Plant-derived acids*

A number of acids of plant origin are sold for insect control. These include citric acid (Fig. 6), recommended for use against a wide range of insects, including ants, aphids, beetles, caterpillars, leafhoppers, mealybugs, mites and whitefly in ornamentals, vegetables, shrubs and fruit trees and sold under the trade name SharpShooter by St Gabriel; fatty acids (often oleic acid – Fig. 6), effective against aphids,

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thrips and scale insects in vegetables, fruit and ornamentals (oleic acid is also a major constituent of neem oil (q.v. Section 4.3.2 on azadirachtin)); and formic acid (Fig. 6), used to control varroa (*Varroa destructor* Anderson & Trueman) and tracheal mites in honey bees. Fatty acids such as oleic acid also have fungicidal uses in grapes, roses and other crops, and herbicidal uses, including total weed control and moss control in lawns.

The mode of action of citric acid is not identified with certainty. Formic acid is a severe irritant and acts by directly killing the mites while not disrupting bee behaviour or life span substantially. Oleic acid interferes with the cell membrane constituents of the target organism, leading to a breakdown of the integrity of the membrane and subsequent death. Different fatty acids are effective as insecticides, fungicides, total herbicides or as moss killers.[2] The products are sold under a wide range of trade names by many different manufacturers.

4.3.8 Pyrethrins, chrysanthemates and pyrethrates

Pyrethrins, chrysanthemates and pyrethrates (Fig. 6) are extracted from the flower of *Tanacetum cinerariaefolium* (Trevisan) Schultz-Bip. (syns. *Chrysanthemum cinerariaefolium* Vis., *Pyrethrum cinerariaefolium* Trevisan). The extract is refined using methanol or supercritical carbon dioxide. The dried, powdered flower of *T. cinerariaefolium* has been used as an insecticide from ancient times. The species was identified in antiquity in China, and it spread to the west via Iran (Persia), probably via the Silk Routes in the Middle Ages. The dried, powdered flower heads were known as 'Persian insect powder'.[4] Records of use date from the early nineteenth century when it was introduced to the Adriatic coastal regions of Croatia (Dalmatia) and some parts of the Caucasus. Subsequently, it was grown in France, the USA and Japan. Plants producing these compounds are now widely grown in East African countries, especially in Kenya (1930), in Ecuador and Papua New Guinea (1950) and in Australia (1980).

The pyrethrins have the CAS registry numbers *[8003-34-7]* for pyrethrins, *[121-21-1]* for pyrethrin I, *[25 402-06-6]* for cinerin I, *[4466-14-2]* for jasmolin I, *[121-29-9]* for pyrethrin II, *[121-20-0]* for cinerin II and *[1172-63-0]* for jasmolin II.

The pyrethrins 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.

They have been shown to bind to and activate the voltage-sensitive sodium channels of nerve, heart and skeletal muscle cell membranes in insect nervous systems, prolonging their opening and thereby causing knockdown and death. They are non-systemic insecticides with contact action. Initial effects include paralysis, with death occurring later. They have some acaricidal activity.[104–106] Pyrethrins are sold in a wide variety of formulations, under many different trade names by a large number of different manufacturers. These include Alfadex from Syngenta; Evergreen, Pyrocide, Premium Pyganic 175, Pyganic Crop Protection EC 1.4 and Pyganic Crop Protection EC 5.0 from MGK; Pyronyl (plus piperonyl butoxide), Prentox Pyrethrum Extract and ExciteR from Prentiss; Milon from Frunol Delicia; Pycon (concentrated mixture with piperonyl butoxide) from Agropharm; Hash (plus piperonyl butoxide) from Kemio; CheckOut from Consep; Py-rin Growers Spray from Wilbur-Ellis; Diatect II, Diatect III and Diatect V (all plus piperonyl butoxide and silica) from Diatect; Bonide Liquid Rotenone/Pyrethrin Spray (rotenone 1.1% plus pyrethrum 0.8%), Garden Dust (pyrethrins 0.03%, rotenone 0.5%, cube resins 1%, copper 5% and sulfur 25%) and Earth Friendly Fruit Tree Spray/Dust (rotenone plus pyrethrum plus sulfur plus copper) from Bonide; Safer Yard and Garden Insect Killer (pyrethrum plus insecticidal soap) from Woodstream; and Ecozone Pyrethrum Insect Powder from Natural Animal Health Products.

It is usual today to apply pyrethrins in combination with synergists (e.g. piperonyl butoxide) that inhibit detoxification within the target insects. In addition, many combination products with other insecticides are available. It is essential to cover the crop foliage well for effective control. Natural pyrethrins are used in home and garden insecticide formulations but are no longer widely used in agricultural crop protection. They are approved for use in organic production.

Pyrethrins have moderate mammalian toxicity, and there is no evidence that the addition of synergists increases this toxicity. The compounds show low toxicity to birds, but are highly toxic to fish and honey bees (although they exhibit a repellent effect to bees).[106–108]

4.3.9 Rotenone

Rotenone (Fig. 6) (BSI, E-ISO, F-ISO, ESA, accepted in lieu of a common name) or derris (JMAF), also known as derris root, tuba-root, aker-tuba (for the plant extract) and barbasco, cube, haiari, nekoe and timbo (for the plants), is obtained from *Derris, Lonchocarpus* and *Tephrosia* species that were used originally in Asia and South America as fish poisons.

Rotenone has the CAS registry number *[83-79-4]*. It is used to control a wide range of arthropod pests, including aphids, thrips, suckers, moths, beetles and spider mites in fruit and vegetable cultivation, for the control of fire ants and of mosquito larvae when applied to pond water and is recommended for the control of lice, ticks and warble flies on animals and for insect control in premises. Rotenone has also found a use in the control of fish populations.

It is an inhibitor of site I respiration within the electron-transport chain of susceptible insects and is a selective, non-systemic insecticide with contact and stomach action and secondary acaricidal activity.[109–112] Rotenone-based products are sold in a wide range of different formulations by different manufacturers under many different trade names. Many of these products are combinations with other insect-active compounds. Typical trade names include Chem Sect, Cube Root, Chem-Fish and Rotenone Extract from Tifa; Vironone from Vipesco; PB-Nox (plus piperonyl butoxide) from Penick; Pyrellin [plus pyrethrins (pyrethrum)] from Wright Webb; Prenfish (mixture), Noxfish, Nusyn-Noxfish (plus piperonyl butoxide) and Synpren Fish (mixture) from Prentiss; and Rotenone 5% Organic Insecticide, Bonide Liquid Rotenone/Pyrethrin Spray (rotenone 1.1% plus pyrethrum 0.8%), Garden Dust (rotenone 0.5%, pyrethrins 0.03%, cube resins 1%, copper 5% and sulfur 25%), Rotenone-Copper Dust and Earth Friendly Fruit Tree Spray/Dust (rotenone plus pyrethrum plus sulfur plus copper) from Bonide. All products are applied as an overall spray to give good coverage of the foliage. Rotenone has been cleared for use in organic farming when insect pressure is very high.

Rotenone has a high mammalian toxicity, with the estimated lethal dose for humans being $300-500\,\mathrm{mg\,kg^{-1}}$. It is more toxic when inhaled than when ingested and is very toxic to pigs. It is not toxic to bees, but combinations with pyrethrum are very toxic. It is very toxic to fish and must not be used near water courses.

4.3.10 *Ryania extract*

The insecticidal activity of ryania was reported by Pepper and Carruth,[113] and it was introduced by SB Penick & Co. These alkaloids from the stem of *Ryania* species, particularly *R. speciosa* Vahl, represent the first successful discovery of a natural insecticide. The collaboration between Rutgers University and Merck in the early 1940s followed the lead from the use of *Ryania* species in South America for euthanasia and as rat poisons. This collaborative work revealed that *Ryania* alkaloid extracts were insecticidal.[113]

Ryanodine (Fig. 6) has the CAS registry numbers *[8047-13-0]* for ryania, *[15 662-33-6]* for ryanodine and *[94 513-55-0]* for 9,21-didehydroryanodine. It was used for control of codling moth (*Cydia pomonella* L.), European corn borer (*O. nubilalis*) and citrus thrips in maize (corn), apples, pears and citrus.

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.[97,114,115] Ryania extracts have had limited use as insecticides, but they do give effective control of selected species. The size and complexity of the natural compound means that it can be used economically only to treat infested crops, and it has no systemic activity. The rapidity of its effect is an advantage in the control of boring insects. More recently the mode of action of ryanodine has attracted the attention of the agrochemical industry, and at least two products with this mode of action are currently under development.[116,117]

It is sold as a DP by AgriSystems International under the trade names Natur-Gro R-50 and Natur-Gro Triple Plus and Dunhill Chemical under the trade name Ryan 50, but all uses in the USA were cancelled voluntarily in 1997. It is applied when insects are attacking the crop, at rates of $10-72\,\mathrm{kg\,ryania\,ha^{-1}}$. Good coverage is essential, but it must not be sprayed near water courses. Ryania extracts are moderately toxic to mammals, but very toxic to fish.

4.3.11 *Sabadilla*

Sabadilla is an insecticidal preparation from the crushed seeds of the liliaceous plant, *Schoenocaulon officinale* Gray (formerly *Veratrum sabadilla* Retr.), which was used by native people of South and Central America as an insecticide for many years. Preparations from various hellebore plants (*Veratrum* spp.) were once used commercially. Its practical use in modern agriculture was revived by the work of Allen *et al*. in the 1940s.[118] Sabadilla has been used commercially since the 1970s. The seeds of *S. officinale* contain a mixture of alkaloids – veratrine, consisting of an approximately 2:1 mixture of cevadine and veratridine (Fig. 6), in combination with many minor components, all of which are esters of the alkamine veracine.[119] The product is produced by grinding the seeds of the plant and subsequent concentration. The seeds contain between 2 and 4% alkaloids.

The CAS registry numbers are *[8051-02-3]* for sabadilla or the veratrine mixture, *[5876-23-3]* for veracevine, *[28 111-33-3]* for cevacine, *[62-59-9]* for cevadine, *[124-80-1]* for sabadine, *[187 237-90-7]* for 3-*O*-vanilloylveracevine and *[71-62-5]* for veratridine.

The compounds are effective against thrips (*Frankliniella* spp. and *Thrips* spp.) in citrus and avocados.[120] Cevadine, veratridine and related cev-eratrum alkaloids have a mode of action that is similar to that of the pyrethrins in that they activate the voltage-sensitive sodium channels of nerve, heart and skeletal muscle cell membranes, although the binding site appears to be different from that of the pyrethroids. They are non-systemic insecticides with contact action. Initial effects include paralysis, with death occurring later.[97,121,122] Sabadilla powder is a contact insecticide that is often mixed with other botanical insecticides for improved biological efficacy.

Sabadilla powder is sold as WP and SL formulations. Some formulations contain sugar as an insect feeding stimulant. The alkaloid content in these formulations varies between 0.2 and 25%. They are sold by Dunhill Chemical under the trade names Veratran D and Veratran. Recommended use rates are between 20 and $100\,\mathrm{g\,ha^{-1}}$ of total alkaloid. Veratridine persists longer than cevadine, but both are degraded in air and sunlight. Consequently, frequent applications and good foliage cover enhance the biological effects. No residual activity against thrips was observed 7 days after treatment. Sabadilla powder is not used widely in crop protection, but it is approved for use in organic farming systems.

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Sabadilla has a low mammalian toxicity, but it is an irritant to mucous membranes, causing sternutatory reactions, and is an irritant to eyes, causing lachrymation and inflammation.[123] Sabadilla powder is not active against beneficial insects and may be used in insect control strategies that use them.[124]

4.3.12 Starch syrup

A new insecticide prepared from reduced starch syrup has just been made available by Kyoyu Agri. Its chemistry has not been characterised and it is included here for completeness. It is sold under the trade name YE-621 and works by obstructing the spiracles of insect pests, causing suffocation. YE-621 is potentially effective against insect pests that are resistant to chemical-based insecticides. It is non-toxic to humans and beneficial insects and/or natural predators. The main component of YE-621 is starch syrup sourced mainly from corn and potatoes, and the other ingredients are water plus surfactant.[125]

4.4 Miscellaneous crop protection agents

4.4.1 Anthraquinone

9,10-Anthraquinone (Fig. 7) (BSI, E-ISO, F-ISO, in lieu of a common name) is found in a wide range of plants including teak (*Tectona grandis* L.), red quebracho [*Quebrachia lorentzii* (Griseb.)] and in the cuticular wax of perennial rye grass (*Lolium perenne* L.). It has the CAS registry number *[84-65-1]*.[126]

Anthraquinone is used as a bird repellent, especially for geese on golf courses and any bird that is likely to endanger aircraft, and seed feeders to safeguard treated crop seed. It is often added to insecticide and/or fungicide-treated seed to protect birds from accidental poisoning.[126]

It has a marked repellent effect on birds, usually inducing retching. Its activity is thought to be due to its extremely bitter taste. The use of the product in airports is intended to disperse birds that may pose threats to aeroplanes. Efficacy data have been submitted to the US-EPA to support claims of anthraquinone's ability to repel blackbirds, geese, cowbirds, robins, starlings, pigeons, horned lark and gulls. However, the review of the data indicated anthraquinone's repellency for geese only. Effects on the other bird species were not supported by the studies submitted. Because anthraquinone is not persistent, regular applications are required to keep the geese away. Anthraquinone-treated seed is usually avoided by seed-feeding birds.

It is sold as dry and wettable powder, flowable and liquid concentrates, solutions and water-dispersible powder seed treatments (often in mixtures) and as a liquid concentrate containing 50% anthraquinone.

Spray applications are made when birds have been determined to be a nuisance. Typical trade names include Corbit and Morkit by Bayer CropScience and Flight Control from Environmental Biocontrol. Applications must be repeated at weekly intervals. Treated seed is sown in the normal way.

Anthraquinone is not considered to be toxic to mammals and is not expected to have any adverse effects on non-target organisms or the environment.[127] However, a recent study has indicated that it is a carcinogen.[128]

4.4.2 Black pepper oil

Oil of black pepper is a pale-yellow irritating liquid with a sharp peppery odour, obtained by steam distillation of the unripe dried fruit (peppercorns) of the black pepper plant (*Piper nigrum* L.). It has the CAS registry number *[8006-82-4]*.

Black pepper oil is used as a repellent for a wide variety of small mammals, including dogs, cats, ground hogs, squirrels, skunks and raccoons. It is used indoors, but only in non-living areas (attics, basements, cellars, storage areas, garages, sheds and barns) and outdoors on lawns, garden paths, flower-beds, ornamental plants, trees, shrubs and garbage bags. The sharp and distinctive odour of the pepper oil is irritating to most target animal species.[2]

No adverse effects to humans are expected from the use of oil of black pepper in small mammal repellent products, because oil of black pepper is considered 'generally recognised as safe' (GRAS) for use in food by the Food and Drug Administration (FDA) and is widely used as a flavouring agent in foods; there is widespread exposure to oil of black pepper without any reported adverse effects to human health; therapeutically, the oil is mixed with other ingredients and applied to human skin with no apparent adverse effects, and very low levels of oil of black pepper are present in the registered end-product, so exposure is expected to be minimal. No toxic effects have been identified in mammals, birds or fish. No adverse effects are expected, based on the widespread use of oil of black pepper and the lack of reported adverse effects. Oil of black pepper is intended to repel small mammals and therefore is not expected to harm target or non-target organisms.

4.4.3 Capsaicin

Capsaicin (Fig. 7) is a common ingredient of solanaceous plants of the genus *Capsicum*. It is the compound responsible for the hotness of these chilli peppers. It is obtained by grinding dried, ripe chilli

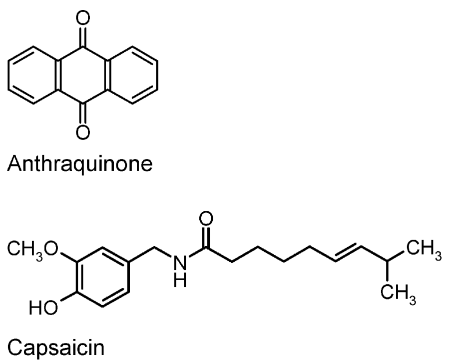

Figure 7. Miscellaneous plant-derived crop protection agents.

peppers (*Capsicum frutescens* L.) into a fine powder. Oleoresin is obtained by extracting the powder in a solvent and evaporating the latter. The resulting highly concentrated liquid has little odour, but has an extremely pungent taste. It is often sold in combination with extracts of garlic, onion, mustard and various herbs. It has the CAS registry number *[404-86-4]*.

Capsaicin is a general insect and mite repellent, but is also claimed to reduce transpiration in treated crops and to repel larger animals.[2] There are claims that, when it is used as a soil drench before planting, it will control a wide range of fungi (including *Pythium, Rhizoctonia, Phytophthora, Pyrenochaeta, Sclerotium, Armillaria* and the clubroot organism, *Plasmodiophora*), soil insects (such as wireworms, cutworms, June beetle, June beetle larvae and white grubs), molluscs, nematodes (including root-knot species *Tylenchus, Pratylenchus, Xiphinema, Criconemoides* and *Paratylenchus*) and some weeds seeds, roots, stolons and bulbs of broad-leaved weeds and grasses, including couch grass [*Elytrigia repens* (L.) Desv.], annual meadow grass (*Poa annua* L.), broomrape (*Orobanche* spp.), fat hen (*Chenopodium album* L.), torpedo grass (*Panicum repens* L.) and bermuda grass (*Cynodon dactylon* Persoon). It is not effective against mallow (*Malva* spp.), dodder (*Cuscuta* spp.) and some species of clover (*Trifolium* spp.). Some products claim repellent effects to phytophagous insects and mites.

Capsaicin is claimed to disrupt insect metabolism and to affect the insect central nervous system. The pepper extract tends to damage the cell membranes of the insect, causing punctures or holes to form. The mustard extract is a neurotoxin, which will penetrate the damaged membrane and exoskeleton of the insect and kill the insect through its neurotoxic effects. Animal repellency effects are due to the pungent odour of the extract and an associated irritancy. Unlike other insect repellents, capsaicin also has some insecticidal activity and can be applied to crops with low levels of insect infestation.

Products are sold in a variety of formulations, under several different trade names including Armorex, Nemastroy and Valoram from Soil Technologies, Bonide Hot Pepper Wax from Bonide, Dazitol from Champon, Hot Pepper Wax from Hot Pepper Wax and Hot Pepper Wax Animal Repellent from Biocontrol Network. Three treatments per season are usually sufficient for long-term control.

These products are composed of compounds extracted from plants used for culinary purposes and are not considered to be toxic to mammals. They are rapidly degraded in the environment, but are toxic to beneficial insects including honey bees.

4.4.4 Cinnamaldehyde

The chemical and biological properties of cinnamaldehyde (Fig. 4) have been described in Section 4.1.1 on plant-derived fungicides. It has animal-repellent and insect-attractant properties that are based on its strong odour.

5 ANIMAL-DERIVED PRODUCTS

5.1 Fungicides and bactericides

5.1.1 Milk

A recent report from Australia has indicated that the application of cow milk to many crop plants infected with powdery mildews is an effective treatment, outperforming many commercial products. It is reported that it is being developed as a commercial treatment.[129]

5.1.2 Poly-D-glucosamine

Poly-D-glucosamine or chitosan is produced from dried, crushed crustacean exoskeletons and is used to control various species of powdery mildews and *Botrytis* in fruit (such as grapes, strawberries, cherries and apple), vegetables (such as cucumbers, squash, pumpkins, peas, peppers and tomatoes) and glasshouse and nursery plants [such as flowers (roses, etc.), potted plants and protected vegetables]. It has the CAS registry number *[9012-76-4]*.

Poly-D-glucosamine is an elicitor that stimulates the natural defence response system in treated plants by binding to fungal receptor sites, thereby mimicking an attack by fungal spores. This, in turn, results in signals being sent to the nuclei of the plant cells. These signals elicit multiple genetic and biological responses, including the production of phytoalexins (antimicrobial compounds produced in plants), aimed at inhibiting fungal infections.[2]

Elexa is a 4% aqueous suspension sold by SafeScience. Poly-D-glucosamine has an excellent toxicity profile and, in the USA, Elexa is an 'exempt from tolerance' product.

5.2 Insecticides, acaricides and nematicides

5.2.1 Poly-N-acetyl-D-glucosamine

Poly-*N*-acetyl-D-glucosamine (Fig. 8) (also known as chitin) is present in the shells of all crustaceans and insects and in certain other organisms, including many fungi, algae and yeast. Commercially, it is isolated from the shells of crustaceans, after the edible parts have been removed. It has the CAS registry number *[1398-61-4]* and is used to control plant pathogenic nematodes in most field crops, ornamentals and turf grown in fields, home gardens and nurseries.

Poly-*N*-acetyl-D-glucosamine is thought to control plant pathogenic nematodes by stimulating the growth of certain naturally occurring microorganisms in soil, which, in turn, release chemicals that kill the pathogenic nematodes and their eggs.[2]

Igene sells Clandosan formulated as pellets and granules. It is applied in the field 2–4 weeks before planting, such that it is concentrated 15–25 cm below the soil surface.

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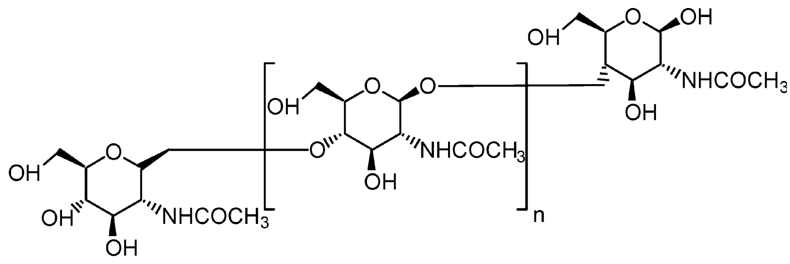

Poly-*N*-acetyl-D-glucosamine

Figure 8. Animal-derived plant protection products.

No risks to humans are expected when products containing chitin are used according to label directions. Chitin is closely related structurally to the active ingredient chitosan (poly-D-glucosamine – see above), which shows no toxicity to mammals and is approved by the Food and Drug Administartion (FDA) as a food additive.

6 CONCLUSIONS

Considering the growing interest in demand for organic production of food, the number of pest management products that can be used in this production is not large. Furthermore, there is a paucity of good published research on best use and efficacy of the products that are available. Few studies have compared the relative cost and efficacy of natural product pest management products with synthetic pesticides. The authors hope that this compendium and review of commercial natural product pest management products will provide researchers with some of the information they will need to plan research to fill this void.

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