Feature

Plant-derived products – a source of new ais

by Dr Alan Baylis

Plants can provide a wealth of biologically active compounds for use in many industries. Dr Alan Baylis looks at options for the crop protection sector.

Today's agriculture is under pressure, not only to provide food, but also fuel and energy from a limited area of land. These demands, together with the development of resistance and ever more stringent regulatory hurdles, are among major drivers for the search for highly active crop protection compounds with new modes of action. The use of plants as sources for such compounds was discussed at a UK Society of Chemical Industry meeting in November.

Natural products provide an excellent source of both activity and diversity, said Dr David Evans, former head of research and technology for Syngenta. Although many plant secondary metabolites have structures that may look like "chicken wire", the array of technologies available to crop protection chemists and screeners today means that natural products should be a significant source of innovative new leads, he added.

However, with more than 350,000 species of plants, searching for useful bioactive compounds can be a daunting task. A knowledge of plant taxonomy can increase success rates, said Professor Monique Simmonds of the Jodrell Laboratory at Kew Gardens (UK). Work has focused mainly on insect behavioural modifiers, particularly non-volatile anti-feedants.

Many better known bio-active compounds are complex molecules and very difficult to synthesise, such as azadirachtin, a triterpenoid from the neem tree (*Azadirachta indica*), and cucurbitacin B, a feeding stimulant used to attract and trap insects, found in cucurbits. These are examples where the Kew team are attempting to characterise functional groups associated with activity and then seek simpler molecules by systematically "mining" plant families.

A suite of 18 screens for useful effects on insects has been developed. These are mainly based on taste perception, such as an electrophysiology bio-assay using the taste sensilla mouthparts of locusts. Screening extracts of species by plant families for anti-feedant activity is highlighting certain families as being especially rich sources. These include the Araceae (2,800 species) and Amaryllidaceae (900 species).

In the Labiatae family, a range of terpenoids have been isolated from bugle (*Ajuga reptans*) and skullcap (*Scutellaria galericulata*) that are promising candidates for controlling African armyworms and desert locusts. Other compounds of interest are the kunzein series from *Kunzea* spp and ficifolidone from eucalyptus.

Nevertheless, a couple of notes of caution were sounded at the meeting. Firstly, nomenclature and place in taxonomy are not always agreed upon, especially among the more obscure plant species. Secondly, it is well known that a plant's secondary metabolite profile can be very different between germination and senescence.

Researchers at the UK University of Portsmouth have been selecting and screening extracts of endophytic fungi for activity against insects, weeds and fungal diseases. Many classes of fungi are intimately associated with plant tissues and although the relationships between them are often unclear, such fungal endophytes are proving to be interesting sources of novel leads.

Selecting plant species from different ecological niches and growing their endophytic fungi on various media are techniques being used to increase both variation and strength of activity on the screens.

Natural products have provided important diversity in leads, starting with the development of synthetic pyrethroid insecticides from pyrethrum (a *Chrysanthemum cinariifolium* extract) at the UK research centre at Rothamsted in the 1950s, to the range of strobilurin fungicides currently available. In the course of their optimisation, a great deal has been learned in meeting challenges such as improving selectivity and soil properties, Dr Evans noted.

The mode of action of the pyrethroids requires highly lipophilic molecules. This also means that they bind tightly to soil organic matter, making them immobile and unable to access and control soil pests. The solution, which resulted in Syngenta's tefluthrin, was to introduce volatility and optimise physical properties for control by the vapour phase.

The strobilurin foliar fungicides were actually inspired by a soil-mediated herbicidal effect. Some woodland fungi secrete strobilurin A, which prevents other fungi

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encroaching too close. Synthetic chemistry and screening programmes at Syngenta's research site at Jealott's Hill worked through 700 compounds from strobilurin A to address photosensitivity, volatility and lipophility, to discover azoxystrobin, the first commercial product in the series.

In herbicides, a recent commercial success story has been the Callisto family of products from Syngenta, based on mesotrione, a benzoylcyclohexanedione or triketone. Mesotrione was launched in 2001 for pre- and post-emergence control of broad-leaved weeds and some grasses in maize, and annual sales are now around $500 million. Dr Glynn Mitchell of Syngenta presented a case study of mesotrione chemistry from inspiration to synthesis of the active ingredient selected for development.

The allelopathic effects of the bottlebrush plant (*Callistemon citrinus*) were noticed in 1977 and found to be due to leptospermone, an acylsyncarpic acid. This natural phytotoxin was active on screens at kilogram per hectare rates with a narrow spectrum and no useful selectivity, but recognised as an interesting lead. The white bleaching symptomology was found to be due to inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), and a programme of analogue synthesis and screening was commenced.

Key steps in optimisation were boosting activity, achieving crop selectivity and reducing soil persistence. Physiological studies found that the substitution pattern affected metabolism in grasses and also determined soil persistence. Understanding this was essential to the development, first of sulcotrione, launched for control of broad-leaved weeds in maize in Europe in 1991, and later its close analogue, mesotrione.

different approaches . . .

When plants are wounded, they often produce chemical signals that ultimately repel or attract insects. Potatoes and cotton produce cis-jasmone when damaged. At Rothamsted, studies have identified a promising system involving the application of cis-jasmone, which induces the production of 6-methyl-5-hepten-2-one, a powerful insect repellent.

Results from field trials on wheat showed that cis-jasmone effectively repelled grain aphids (*Sitobion avenae*), an important vector of barley yellow dwarf virus, reported Professor John Pickett. Cis-jasmone does not seem to depress crop yields as is the case with methyljasmonate and has the advantage of being listed as a food additive. However, the wheat variety involved is important to the magnitude of the effect.

Other natural compounds of interest include the volatile sesquiterpenes, (E)-ß-farnesene and germacrene D. (E)-ß-farnesene is used by many aphid species as an alarm pheromone to warn related individuals of predator attack. Differences in insect response to the enantiomers of such compounds are well known. Goldenrod (*Solidago canadensis*) is a useful source of germacrene D because, unusually, it produces both enantiomers, one of which is ten times more active than the other.

essential oils . . .

Essential oils, or distilled volatiles from plants, have been used as broad-spectrum, non-selective insecticides for possibly many centuries. David Marks of Plant Impact presented trial results for a mixture of essential oils currently in the process of being registered for the control of whiteflies, mites, aphids and thrips on fruit and vegetables (*Agrow* No 490, p 19). Plant Impact expects a registration for its Bug Oil insecticide to be granted by the US EPA in early 2008, with European registrations to follow, first in the UK and Germany.

Bug Oil is a mixture of essential oils from *Thymus vulgaris* (0.5%), *Tagetes erecta* (0.5%) and *Gaultheria procumbens* (0.1%) dissolved in rapeseed oil. The mixture allows low, non-phytotoxic rates of individual components with complementary insecticidal and behavioural effects. The environmental profile is good, with any residues being indistinguishable from naturally occurring compounds, Mr Marks pointed out.

◆ *Dr Alan Baylis of Nuvistix Innovation contributed this article. The SCI conference, Plant-derived Natural Products – A Resource for Bioactive Compounds, was held on November 28th 2006 at Syngenta's Jealott's Hill International Research Centre, UK.*