doi: 10.17221/31/2016-PPS

History, Presence and Perspective of Using Plant Extracts as Commercial Botanical Insecticides and Farm Products for Protection against Insects – a Review

Roman PAVELA

Department of Secondary Plant Metabolites in Crop Protection, Division of Crop Protection and Plant Health, Crop Research Institute, Prague, Czech Republic

Abstract

Pavela R. (2016): **History, presence and perspective of using plant extracts as commercial botanical insecticides and farm products for protection against insects – a review**. Plant Protect. Sci., 52: 229–241.

Botanical insecticides keep attracting more attention from environmental and small farmers worldwide as they are considered as a suitable alternative to synthetic insecticides. The use of secondary metabolites in a defensive manner isolated from plants is a tradition more than 3000 years old. However, despite current intensive research, the assortment of suitable commercial products is very limited and insufficient in view of the global rise in the demand for biopesticides. Farm products as well as new basic substances offer an important perspective of being widely used in the protection against harmful insects due to their multiple undoubted benefits. These benefits, which are also drawbacks of botanical insecticides, as well as their history in addition to their presence and perspective are critically reviewed in this paper.

Keywords: medicinal plants; essential oils; Azadirachta; Pyrethrum; mechanism of action

The role of insecticides in human society is very important. We are talking not only about agricultural production where they are used to eliminate damage caused by phytophagous insects but also about human health coupled with the health of domesticated animals where insecticidal substances are used to reduce the population density of vectors.

Phytophagous insects can cause very significant damage to grown crops, which may range anywhere between 10 and 90% (with an average of 35–40%) for all potential food and fibre crops (Pavela *et al*. 2007; Weinberger & Srinivasan 2009). The amount of losses caused by pests depends on many factors such as the grown species in addition to the variety, climatic and pedological conditions, plant nutrition, and population density of the pests or low incidence of their natural enemies (Grzywacz *et al*. 2014). Besides the losses which are caused directly during the process of growing crops in fields, storage pests may subsequently cause damage to the harvests stored in granaries and storehouses (Stevenson *et al*. 2014). Considering the fact that the world population is expected to grow to nearly 10 billion by 2050 and the fact that there is a falling ratio of arable land for the growing population, the use of pesticides in agricultural production remains a topical issue.

The protection of human and animal health against diseases transmitted by insects is also important and difficult to manage without insecticides. In particular, some mosquito species (above all species belonging to the genera *Culex* spp., *Aedes* spp., and *Anopheles* spp.) are important disease transmitters. Passing from host to host, some transmit extremely harmful diseases such as malaria, dengue, leishmaniasis, filariasis, and Chagas disease. Furthermore, the recent outbreaks of Zika virus infections, occurring in South America, Central America and the Caribbean, represent the most recent four arrivals of important arboviruses in the Western Hemisphere, over the last

Supported by the Ministry of Agriculture of the Czech Republic, Project No. QJ1510160.

doi: 10.17221/31/2016-PPS

20 years (Benelli & Mehlhorn 2016). These can cause extensive morbidity and mortality in addition to being a major economic burden within disease-endemic countries (WHO 2009a, b, 2012a, b, c).

Malaria, in particular, continues to impart a major disease burden on infants and young children in endemic regions. There are 350 to 500 million cases of malaria annually causing at least 1 million deaths. 90% of the mortality rate attributed to malaria is experienced by infants and young children as the vast majority comes from sub-Saharan Africa (Tolle 2009; WHO 2009a, 2012b). Moreover, recently, a significant association of malaria incidence with all cancer mortality in 50 U.S. states was highlighted and may be explained by the ability of *Plasmodium* to induce suppression of the immune system. However, it was hypothesized that *Anopheles* vectors may transmit obscure viruses linked with cancer development. The possible activation of cancer pathways by mosquito feeding events is not rare. For instance, the hamster reticulum cell sarcoma can be transmitted through the bites of *Aedes aegypti* by a transfer of tumour cells. Furthermore, mosquito bites may influence human metabolic pathways following different mechanisms, leading to other viral infections and/or oncogenesis (Benelli *et al*. 2016).

Likewise, dengue ranks among the mosquito-borne viral diseases in the world. In the last 50 years, the incidence has increased 30-fold. An estimated 2.5 billion people live in over 100 endemic countries and areas where dengue viruses can be transmitted. Up to 50 million infections occur annually with 500 000 cases of dengue haemorrhagic fever resulting in approximately 22 000 deaths, mainly among children (WHO 2012a). Based on estimates from the World Health Organization, approximately 2 million people succumb annually to diseases transmitted by mosquitoes.

Although on the one hand, insecticides play an important role in the development of human society, on the other side we should have concerns about their frequent use which keeps rising. The four main groups of insecticides such as the organochlorine, organophosphate, carbamate, and pyrethroid insecticides are of a particular concern because of their toxicity and persistence in the environment. Therefore, their use is being gradually abandoned (Smith & Gangolli 2002; Walker & Lynch 2007). However, several of the banned pesticides are still used on a large scale in developing countries and continue to pose severe health as well as environmental problems (Stoytcheva 2011).

According to the WHO's estimate, 3 million cases of pesticide poisoning occur every year, resulting in more than 250 000 deaths, mostly due to inexpert handling and application or intentional poisoning (Stoytcheva 2011). Concerns about the negative impact of pesticide residues on human and animal health are based on many scientific studies that have indicated the harmful effects of some synthetic active substances of pesticides. For example, a number of epidemiological studies have been carried out to evaluate the association between exposure to pesticides and cancer (Settimi *et al*. 1990; Wolff *et al*. 1993; Dewailly *et al*. 1994). It was found that pesticides can play a role in the cancer process by either non-genotoxic mechanisms such as promotion, peroxisome proliferation, and hormone imbalance, or by affecting the carcinogenic process in a variety of ways, of which both can alter the genome and provide a growth advantage for neoplastic cells (Hodgson & Levi 1996; Stoytcheva 2011).

Some insecticides have negative effects on the nervous, renal, respiratory and reproductive systems of men and women (Stoytcheva 2011). Because of the basic similarities between the mammalian and insect nervous systems, insecticides (organochlorines, OPs, and carbamates) are designed to attack an insect's nervous system and are capable of producing acute, chronic neurotoxic effects in mammals (Tanner & Longston 1990).

Besides a direct negative effect of active substances of synthetic pesticides on human and animal health, excessive or improper use of insecticides is also associated with:

– Pesticide resistance in some pests;
– Water, soil and air contamination that transfers chemical residues along the food chain;
– Reduction of biodiversity and nitrogen fixation;
– Destruction of marine and bird life and/or contributing genetic defects in subsequent generations;
– Changes in the natural biological balances, by means of a reduction of beneficial and non-target organisms and insects, including predators as well as parasites of pests in addition to honeybees (Stoytcheva 2011; Naqqash *et al*. 2016).

On the other hand, the human population is exposed to these chemicals primarily through the consumption of pesticide contaminated farm products, leading to long-term health hazards. Pesticides may induce oxidative stress leading to the generation of free radicals and alteration in antioxidant or oxygen free radical scavenging enzymes such as superoxide dismutase,

doi: 10.17221/31/2016-PPS

catalase, glutathione peroxidase, glutathione reductase, and glutathione transferase (Ahmed *et al.* 2000).

These problems associated with the use of synthetic insecticides have driven legislative changes (EU Commission 2009), aimed at reducing the consumption of pesticides to a necessary minimum and at replacing risky products with alternative modes of protection against insects.

Currently, several alternatives exist which can provide an efficient control of pests and vectors, and which have been developed by applying the results of research focused on genetic engineering and breeding of plants, or which utilise, for example, the knowledge of plant-pest-predator interactions (Bakhsh *et al*. 2015). The use of plant secondary metabolites synthesised by some plant species as part of their natural self-defence against pathogens and pests seems to be an excellent alternative (Miresmailli & Isman 2014).

Some plants have evolved a wide range of physical and chemical defences against a variety of insects. These substances (e.g. phenols and polyphenols, terpenoids, alkaloids) can be isolated using various extraction methods, including simple maceration of the plant material in water, extraction using organic solvents of various polarities, supercritical fluid extraction, or various types of distillation (Dubey 2011). Some plant extracts have thus become "active substances" of the so-called botanical insecticides (Regnault-Roger *et al*. 2012; Isman & Grieneisen 2014; Pavela 2015a).

This paper presents a critical summary of the most important knowledge concerning botanical insecticides (BIs) and their potential uses.

History of using botanical insecticides

Although the history of using BIs has not been mapped very well, we do know from various existing historical sources that in Europe, the use of some plants in protection against insects dates back more than 3000 years. Primarily, people used various modified parts of some aromatic plants and their extracts or decoctions, particularly as repellents against troublesome insects such as anthelmintics or ectoparasites (Isman 2006; Benelli *et al*. 2015). Plants were also used to protect stored harvests or foods against storage pests (Isman 2006; Grzywacz *et al*. 2014).

Historically, the use of finely ground chrysanthemum (*Chrysanthemum cinerariaefolium*) flowers can be mentioned as the best-known example. According to preserved written documents, this plant played a very important role in the efforts to fight against obligatory ectoparasites such as louses and fleas. There are reports that in 400 B.C., during the Persian king Xerxes' reign, the delousing procedure for children was with a powder obtained from the dry flowers of a plant known as pyrethrum (Abd El Ghany 2012).

In Ancient Rome, granaries were often fumigated with various aromatic plants (for example, rosemary, myrrh, juniper). Aromatic plants were also hung near the entry openings of the granaries. As a result, people learned about the repellent effects of aromatic plant substances (Dubey 2011). The use of poisoned baits prepared as decoctions of *Helleborus niger* L. roots against rodents are also known to have come from this time period. In Persia, various plant oils were used for the treatment of scabies caused by some mites such as *Sarcoptes scabiei* L., 1758 (El-Wakeil 2013).

Later, some plants also started to be used for protection against phytophagous pests, with the development of intensive agricultural production. The first commercial product – botanical insecticide, used as such, dates back to the 17th century when it was shown that nicotine obtained from tobacco leaves would kill plum beetles. Around 1850, a new plant insecticide known as rotenone was introduced. It was obtained from the roots of plants called timbó – *Derris* spp. (Abd El Ghany 2012). In Europe, the further development of commercial BIs was prevented after World War II, when these products were displaced by cheap synthetic insecticides based on organochlorines and organophosphates (Ware & Whitacre 2004). On other continents, this tradition has been preserved only to a limited extent today.

Presence of botanical insecticides

Botanical insecticides can be classified in two major groups according to their production.

(I) The first group includes BIs that are not distributed commercially but are classified as the so-called farming products. These products are produced by farmers or other growers themselves according to preserved traditional recipes passed on for generations. People thus use the knowledge of pesticidal effects of some plants passed on for generations, which are usually found in the area of their local use (Grzywacz *et al*. 2014; Sola *et al.* 2014). It is therefore difficult to evaluate the amount of used plant species utilised for the purposes of making traditional products. However, several ethnobotanical studies

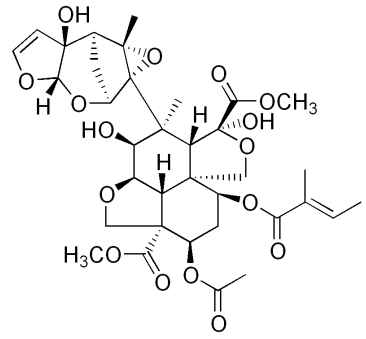
doi: 10.17221/31/2016-PPS

have tried to map information about the utilisation of local flora in the protection against insects (Belmain & Stevensen 2001; Asase *et al*. 2005; Odalo *et al*. 2005).

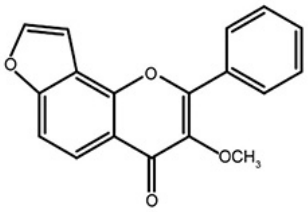
In recent years, the economic difference between chemical protection and protection using farming products has also been studied. For example, Mikenda *et al*. (2015) found out that extracts made from four abundant weed species found in northern Tanzania, *Tithonia diversifolia* (Hemsl.) A. Gray, *Tephrosia vogelii* Hook.f., *Vernonia amygdalina* Delile and *Lippia javanica* (Burm.f.) Spreng, offered the effective control of key pest species on common bean plants (*Phaseolus vulgaris* L.) that was comparable to the pyrethroid synthetic, a.i. lambda-cyhalothrin. Plant pesticide treatments had significantly lower effects on natural enemies (lady beetles and spiders). Plant pesticide treatments were more cost effective to use than the synthetic pesticide where the marginal rate of return for the synthetic was not different from the untreated control (around 4 USD /ha) compared to a rate of return of around 5.50 USD/ha for plant pesticide treatments. This finding is important especially for extensive or environmental agriculture in areas where growers have a sufficient amount of plants suitable for the preparation of extracts in the vicinity of their farms.

(II) The second group of BIs includes commercially manufactured products. These BIs are usually produced by rather small companies, often of local importance only. Although numerous products are produced today, they are usually developed based on active substances (Figure 1) obtained only from a few plant species (Table 1).

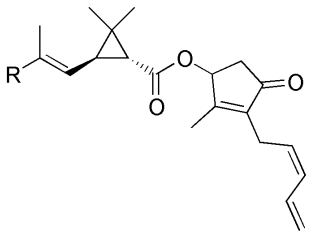
If we should evaluate the importance of BIs according to their share in the global market, Neem products would probably be at the first place, which are based on oil from the seeds of *Azadirachta indica* Juss. (Meliaceae). Limonids were identified as the active components in neem extract. Azadirachtin A-G, nimbin, deacetylsalannin, salannin and their derivatives were reported as the major bioactive metabolites, while their insecticidal, antifeedant, antiovipositant, and repellent (Sidhu *et al.* 2003; Isman 2006; Pavela *et al*. 2009; Benelli 2015b)



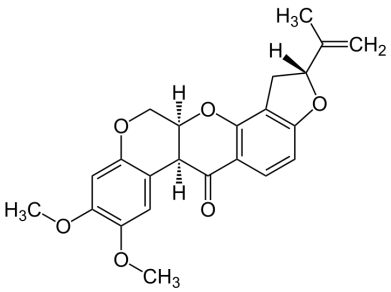
Azadirachtin A



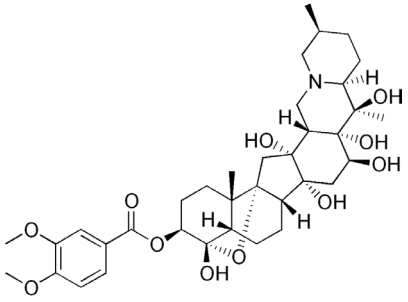
Karanjin



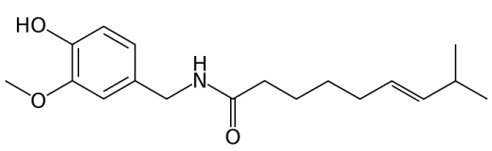
Pyrethrin I, R = CH_3
Pyrethrin II, R = CO_2CH_3



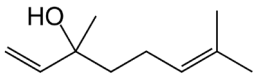
Rotenone



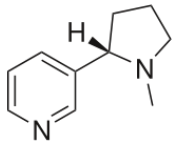
Veradrine



Capsaicin



Linalool



Nicotine

Figure 1. The structure of active ingredients of some botanical insecticides

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doi: 10.17221/31/2016-PPS

Table 1. Examples of the most common commercially produced botanical insecticides

Species (Family)	Active compounds	E.g. comercial produts (company)	Mode of action
Allium sativum L. (Liliaceae)	sulphur compounds e.g. diallyl trisulfide, diallyl disulfide, methyl allyl trisulfide	AjoNey (Invernaderos Hidroponicos Neisi, Mexico); EcoA-Z®, L'EcoMix® or CapsiAlil® (EcofloraAgro, Colombia)	The garlic has a non-toxic mode of action for repelling target birds and insects
Annona squamosa L. (Annonaceae)	squamocin (annonin), debitterized annona oil	ANOSOM® (Agri Life, India)	Mode of action studies revealed that dunnione exhibits both insecticidal and fungicidal activity by inhibiting mitochondrial Complex III
Azadirachta indica Juss. (Meleaceae)	azadirachtin, salanin, nimbin	MARGOSOM® (Agri Life, India); Molt-X® (BioWorks, Inc., USA); NeemAzal T/S (Trifolio-M, Germany); AZERA™(MGK®, USA)	Azadirachtin (and other tetratepenoids) significantly inhibits the activity of AChE in insects. AChE-EC is a key enzyme responsible for terminating the nerve impulse by catalyzing the hydrolysis of neurotransmitters in the nervous system Recently, azadirachtin was categorized as an anti-mitotic (G2/M phase of cell division) insecticide. Studies using radio-labeled azadirachtin have indicated its specific localizations to corpus cardiacum
Capsicum annum L. (Solanaceae)	protoalkaloids e.g. capsaicin	Hot Pepper Wax (Rincon-Vitova Insectaries, USA); ChileNey (Invernaderos Hidroponicos Neisi, Mexico)	In insects, capsaicin causes metabolic disruption, membrane damage and nervous system failure. Also has physical repellent action
Celastrus angulatus Maxim. (Celastraceae)	sesquiterpene pyridine alkaloids	CELAN-X SL (Marketing Arm International, Inc., USA)	Not identified
Citrus × *sinensis* (L.) Osbeck (Rutaceae)	limonene and linalool	Demize EC (Paragon Professional Pest Control Products, U.SA); Prev-Am (Oro Agri SA (Pty) Ltd., South Africa)	The neurotoxic mode of action; most prominent symptoms are hyperactivity followed by hyperexcitation leading to rapid knock down and immobilization. For linalool was identified as an inhibitor of acetylcholinesterase
Chrysanthemum cinerariaefolium (Trevir.) Vis. (Asteraceae)	pyrethrins (cinerins; jamolins and pyerethrins)	Spruzit® (Neudorff, Germany); PyGanic® Crop Protection EC 5.0 or AZERA™ (MGK®, USA); 1.5% Aphkiller AS (Beijing Kingbo Biotech Co., Ltd, China)	Pyrethrins exert their toxic effects by disrupting the sodium and potassium ion exchange process in insect nerve fibers and interrupting the normal transmission of nerve impulses. Pyrethrins insecticides are extremely fast acting and cause an immediate "knockdown" paralysis in insects
Lonchocarpus spp., *Derris* spp. (Fabaceae)	rotenone	5.% Rotenone ME (Beijing Kingbo Biotech Co., Ltd, China); Rotenone Dust (Bonide Products, Inc, USA)	Rotenone exerts as inhibitor of cellular respiration (mitochondrial complex electron transport inhibitor), causing rapid cessation of feeding. Death occurs several hours to a few days after exposure
Nictiana tabacum L. (Solanaceae)	nicotine	Nico Dust or Nico Neem (Nico Orgo Manures, India); 10% Nicotine AS (Beijing Kingbo Biotech Co., Ltd., China)	It competes with acetylcholine, the major neurotransmitter, by bonding to acetylcholine receptors at nerve synapses and causing uncontrolled nerve firing. This disruption of normal nerve impulse activity results in rapid failure of those body systems that depend on nervous input for proper functioning
Pongamia pinnata (L.) Pierre (Fabaceae)	karanjin, debitterised karanjin oil	DERISOM® (Agri Life, India); RockEffect (Agro CS a.s., Czech Republic)	Pongam oil is complex mixtures of biologically active materials, and they are difficult to pinpoint the exact modes of action of various extracts or preparations. In insects is most active as a feeding deterrent, but in various forms it also serves as a repellent, growth regulator, oviposition (egg deposition) suppressant or sterilant
Schoenocaulon officinale A.Gray (Melanthiaceae)	cevadine; veratridine	VERATRAN D® (MGK®, USA)	In insects, sabadilla's toxic alkaloids affect nerve cell membrane action, causing loss of nerve cell membrane action, causing loss of nerve function, paralysis and death

doi: 10.17221/31/2016-PPS

effects have been reported as well. Commercial BIs based on emulsified neem oil may differ considerably in their efficacies because the content of azadirachtin in the oil may range anywhere between 0.01 and 0.9% depending on the ecotype and/or extraction conditions of the seeds (Ramesh & Balasubramanian 1998; Jadeja *et al*. 2011). For this reason, some companies approached the standardisation of their products by adding azadirachtin A, which has a major portion among the contained limonoids and is considered as the most efficient (Sidhu *et al.* 2003). For example, the product NeemAzal T/S from the German company Trifolio-M is sold the most in Europe with a declared content of 10 000 ppm of Azadirachtin A (Pavela *et al*. 2009). Balanced results in insecticidal efficacy are achieved in enriched products. In general, Neem products act especially in the juvenile stages of insects because the main mechanism of action (azadirachtin) impairs the homeostasis of insect hormones by blocking PTTH release from corpora cardiaca (Dwivedi 2008). It only takes a few molecules of azaA to cause irreversible changes in the hormonal activity of insects, resulting in morphological abnormalities in the ecdysis period, which are incompatible with the life of the insect. AzaA is also received very well by the root system and subsequently, it is systematically distributed through xylem into the green parts of plant tissues and stored in leaves in an unchanged form. As has been found out, even a very low content of AzaA in plant tissues may lead to a significant reduction of plant damage by feeding phytophagous pest larvae (Kumar & Poehling 2006; McKenzie *et al.* 2010; de Carvalho *et al*. 2015). For example, this phenomenon can be utilised by applying Neem Cake in soil, applying Neem products by injecting them in the vascular bundles of trees, applying a hydroponic solution or in soil by watering (Pavela & Barnet 2005, 2013b). Currently, Neem products belong to the most favourite BIs and they are applied for the protection of all agricultural crops against all juvenile stages of insects.

Other commonly used products are based on extracts from *Chrysanthemum cinerariifolium* (Trevir.) Vis. (Asteraceae) flowers. As mentioned above, these products have been used for at least 3000 years in Europe. In the past, the flower powder of these plants was especially used in its application against various endoparasites. However, extracts are used more commonly at the present time. As late as in the 18th century, plants designated for the production of these BIs came from plantations in Dalmatia. This is why products against louses and fleas were often sold as "Dalmatian Powder". However, currently most of the world's pyrethrum crop is grown in Kenya, Tanzania, and Australia (El-Wakeil 2013; Sola *et al*. 2014). The term "pyrethrum" is the name for the crude flower dust itself and the term "pyrethrins" refers to the six related insecticidal compounds; three esters of chrysanthemic acid and three esters of pyrethric acid. Among the six esters, those incorporating the alcohol pyrethrolone (namely pyrethrins I and II) are the most abundant and account for most of the pesticidal activity. Technical grade pyrethrum, the resin used in formulating commercial pesticides, typically contains from 20% to 25% of pyrethrins (Casida 1973; Isman 2006; Ramirez *et al*. 2013). The insecticidal action of pyrethrins is characterised by a rapid knockdown effect, particularly in flying insects, and hyperactivity as well as convulsions in most insects. These symptoms are a result of the neurotoxic action of pyrethrins which block the voltage-gated sodium channels in nerve axons.

Pyrethrins are especially labile in the presence of the UV component of sunlight, a fact that has greatly limited their use outdoors. A recent study indicated that the half-lives of pyrethrins on field-grown tomato and bell pepper fruits were 2 h or less (Antonious 2004). This problem created the impetus for the development of synthetic derivatives ("pyrethroids") that are more stable in sunlight. The modern pyrethroids, developed in the 1970s and 1980s, have been highly successful and represent one of the rare examples of synthetic pesticide chemistry based on a natural product model. BIs based on pyrethroids are especially used against small phytophagous insects such as aphids, whiteflies, red spider mites, thrips, hatching insect larvae or against various vectors such as flies and mosquitoes.

Another group of commercial BIs, commonly used today, includes products based on essential oils (EOs). Currently, EOs are considered as a very promising group of secondary plant metabolites suitable for the development and production of BIs (Regnault-Roger *et al*. 2012; Pavela *et al*. 2014; Pavela 2015a). More than 3000 species of aromatic plants are known today, of which about 10% are used commercially as fragrances and flavourings in the perfume as well as food industries, respectively, in addition to being used more recently for aromatherapy and also as herbal medicines (Bakkali *et al.* 2008). The EOs are generally composed of complex mixtures of monoterpenes, biogenetically related phenols, and sesquiterpenes. They are also composed of several dozen substances where the major portion

doi: 10.17221/31/2016-PPS

is usually represented by 1 to 3 substances. These substances often exhibit mutual synergistic effects. Thanks to the knowledge of this phenomenon, which has been a subject of research in recent years, the production of these BIs can be not only standardised, but also their biological efficacy can be enhanced (Pavela 2014b, 2015b). Moreover, some aromatic substances can significantly increase the insecticidal efficacy of synthetic insecticides, which has been shown, for example, for a mixture of EOs with synthetic pyrethroids (Fazolin *et al.* 2016). Several dozen BIs based on various EOs are available in the market. Individual BIs usually contain mixtures of several EOs as active substances which are obtained from various aromatic plants. Manufacturers thus utilise the synergistic action of EOs precisely to enhance the insecticidal effect. The most widely used EOs for BIs are obtained from *Rosmarinus officinalis* L., *Mentha* spp., *Cymbopogon schoenanthus* (L.) Spreng., *Thymus vulgaris* L., *Syzygium aromaticum* (L.) Merrill & Perry, and *Citrus* spp. Examples of some successful products are presented in Table 2.

EOs act very rapidly, not only upon contact, but also through fumigation which has been used for the production of stored products against storage pests (Rattan 2010). In addition, some EOs exhibit significant repellent effects against various species of insects including vectors (Isman 2006; Bakkali *et al.* 2008; Pavela 2011b, c). EOs and their constituents affect biochemical processes, which specifically disrupt the endocrinologic balance of insects. They may be neurotoxic or may act as insect growth regulators, thus disrupting the normal process of morphogenesis (Reynolds 1987). The neurotoxicity of several monoterpenoids (D-limonene, myrcene, terpineol, linalool, and pulegone), which have been identified as important components of essential oils, was evaluated against the housefly as well as on the German cockroach (Coats *et al*. 1991). Singh and Aggarwal (1988) found himachalol and β-himachalene toxic to the pulse beetle. Toxicity of essential oils or their constituents in insects and other arthropods points to a neurotoxic mode of action; the most prominent symptoms are

Table 2. Examples of commercially produced insecticides on base essential oils

Comercial name (Company)	Contains essential oils (%)	Recommended use
Insect Repellent (EcoSMART®, USA)	rosemary (0.5), cinnamon leaf (0.5), lemongrass (0.5), geraniol (1.0)	as repels mosquitoes, ticks, gnats.
Bed Bug Killer for Travel (EcoSMART®, USA)	peppermint (1.5), rosemary (1.5)	against Bed Bug Killer
Mosquito Fogger (EcoSMART®, USA)	geraniol (3.0), rosemary (2.0), peppermint (0.4)	against kills and repels mosquitoes, flies, gnats, moths and other flying insects
Flying Insect Killer (EcoSMART®, USA)	peppermint (2.0), cinnamon (1.0), sesame (1.0)	against kills flies, gnats, mosquitoes, moths, wasps, and other flying insect pests on contact
Home Pest Control (EcoSMART®, USA)	clove (1.0), rosemary (1.0), peppermint (1.0), thyme (0.5)	against ants (including Carpenter, Red Harvester, Pavement and Argentine), beetles, centipedes, cockroaches, crickets, earwigs, fleas, millipedes, pantry pests, pillbugs, silverfish, spiders, sowbugs, ticks and other crawling insect pests
Requiem EC (Bayer AG, Germany)	*Chenopodium ambrosioides* (16.75)	against silverleaf whitefly, trips, psylla
Garden Insect Killer (EcoSMART®, USA)	rosemary (0.25), peppermint (0.25), thyme (0.25), clove (0.25)	kills and repels garden insects and mites; kills exposed eggs, larvae and adult stages
EcoVia WD (Rockwell Labs Ltd., USA)	thyme (10.0)	against ants and termite , biting flies, blow flies, bat bugs, bed bugs, carpet beetles, cigarette beetles, clothes moths, cluster flies, cockroaches, flour beetles, crickets, darkling beetles, dermestids, drain flies, dung flies, scorpions, silverfish, spiders, springtails, stable flies, stink bugs, ticks, wasps, aphids and their eggs, armyworms, bagworms, japanese beetles. lace bugs, mealybugs, mole crickets, mites, caterpillars, thrips, and whiteflies and their eggs

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hyperactivity followed by hyperexcitation leading to a rapid knockdown and immobilisation (Enan 2001).

Despite the rapid effect of aromatic terpenes on insects, EOs do have some drawbacks. In particular, these substances are very instable in the environment; they diffuse rapidly in the environment and thereby the persistence of their effect is noticeably reduced (Turek & Stintzing 2013). For example, these drawbacks are currently addressed using various methods of EO encapsulation (de Oliveira *et al*. 2014; Majeed *et al*. 2015).

To a lower extent, BIs are also produced based on other extracts from *Allium sativum* L., *Annona squamosa* L., *Capsicum annum* L., *Celastrus angulatus* Maxim., *Lonchocarpus* spp., *Derris* spp., *Nicotiana tabacum* L., *Pongamia pinnata* (L.) Pierre, *Schoenocaulon officinale* A.Gray, and *Sophora japonica* (L.) Schott (Table 1). These plants and their potential uses in the protection against insects have been well described in several previous reviews (e.g. Isman 2006; Rosell *et al*. 2008; El-Wakeil 2013). Among these plants, products based on oil obtained from the seeds of an Indian plant, *Pongamia pinnata* (L.) Pierre, seem to offer the highest perspective. This oil contains 5–6% of flavonoids, among which the major portion is represented by the furanoflavonoid karanjin (about 2%). This substance is considered responsible for the insecticidal, antiovipositional, antifeedant and inhibitory effects of pongam oil (Pavela & Herda 2007). Products based on pongam (karanjin) oil are applied against all phytophagous pests.

Perspective of botanical insecticides

BIs exhibit a number of positive aspects that cannot be ignored even by strict advocates of synthetic products. Their environmental safety is one of their main positive aspects. Although their opponents often object that BIs may contain non-selective substances that may have a negative impact on non-target organisms, many tests have shown that upon properly targeted application, the active substances of BIs are very friendly to many non-target organisms (Asogwa *et al*. 2010; George *et al*. 2010; Issakul *et al*. 2011; Pavela 2013a, 2014a). Given that the active substances are natural secondary metabolites of the plants, BI residues are degraded easily and rapidly through natural degradation mechanisms (Turek & Stintzing 2013; Fernandez-Perez *et al*. 2015; Flores-Cespedes *et al*. 2015). This fact is moreover amplified in farming products or basic substances where no extraneous carriers and emulsifiers are used. Another undoubted positive aspect is that BIs (apart from exceptions) contain extracts from plants which do not contain any substances toxic to homeothermic animals. Table 3 provides some toxicological data of the most commonly used active substances of BIs. Products based on plant extracts usually contain synergistically acting mixtures of active substances that exhibit various mechanisms of action (Table 4), which prevents the development of resistant pest populations (Isman 2006; Miresmailli & Isman 2014). Another finding that is not only interesting but also important is that much higher biodiversity as well as frequency of pollinators and natural enemies of pests are seen in crops treated with plant extracts unlike crops which are treated using synthetic insecticides (Amoabeng *et al*. 2013; Mikenda *et al*. 2015).

These positive aspects confirm the strong belief that BIs should play an important role in the fight against harmful insects. This is why every year scientists come up with new information about the insecticidal effects of plant metabolites. Based on the number of scientific studies focused on the research of plant substances with insecticidal effects, it seems that commercial BIs should occupy an important position in the market. Although research of secondary plant metabolites is rising and has seen its rebirth (Isman 2015), there is very little scientific knowledge which has been applied in practice. This is due to several reasons.

(I) ***Lack of suitable plant material***. Many perspective plants are extremely difficult to grow in such a way that they could provide a sufficient amount of high-quality material suitable for the isolation of active substances. Therefore, most commercial

Table 3. Toxicity of certain active ingredients of some botanical pesticides (in mg/kg)

Generic name	Oral LD_{50}	Dermal LD_{50}
Nicotine	50–60	50
Rotenone	60–1.500[a]	940–3.000
Sabadilla	4.000	–
Ryania	750–1.200	4.000
Pyrethrins	1.200–1.500	> 1.800
D-Limonene	> 4.000	> 5.000
Linalool	2.440–3.180	3.578–8.374
Neem oil	> 5.000	> 2.000
Pongam oil	> 4.000	> 2.000

[a]toxicity varies greatly depending on type of solvent used as carrier

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Table 4. Mechanism of action of pesticides of plant origin (modified from Rattan 2010)

System	Mechanism of action	E.g. compounds	E.g. plant source
Cholinergic	inhibition of acetylecholinestrase (AChE)	essential oils, alpha-chaconine	*Mentha* spp., *Lavendula* spp.
	cholinergic acetylcholine nicotinic receptor Agonist/antagonist	nicotine	*Nicotiana* spp., *Haloxylon salicornicum*, *Stemona japonicum*
GABA	GABA-gated chloride channel	thymol, silphinenes, carvacrol	*Thymus vulgarit*, *Senecio palmensis*
Mitochondrial	aodium and potassium ion exchange disruption	pyrethrins	*Crysanthemum cinerariaefolium*, *Chrysanthemum coccineum*
	inhibitor of cellular respiration(mitochondrial complex I electron transport inhibitor (METI)	rotenone	*Lonchocarpus* spp., *Derris* spp.
	affect calcium channels	byanodine	*Ryania* spp.
	affect nerve cell membrane action	sabadilla	*Schoenocaulon officinale*
Octopaminergic	octopaminergic receptors	essential oils	*Cedrus* spp., *Pinus* spp., *Citronella* spp., *Eucalyptus* spp.
	block octopamine receptors by working through tyramine receptors cascade	thymol	*Thymus vulgaris*, *Origanum vulgare; Monarda* spp.
Miscellaneous	hormonal balance disruption	azadirachtin, 20-hydroxyecdysteroid	*Azadiractina indica*, *Leuzea carthamoides*

products are manufactured only from a few plant species that provide sufficiently high yields (Isman 2014; Pavela *et al*. 2016).

(II) ***Insufficient support from the government***. The greatest problem encountered by potential as well as existing BI producers is the costly and lengthy registration process of developed products, often criticised by specialists (Grzywacz *et al*. 2014; Isman 2015). Very strict criteria for the registration of pesticides have been set in some countries including EU states; the criteria have been tightened up in order to avoid environmental and health problems (Settimi *et al*. 1990; Stoytcheva 2011; Sola *et al*. 2014). BIs are thus viewed as critically as synthetically produced substances, even though they are products that often contain the same substances as, for example, commonly used herbal teas or spices. While on the one hand, biofoods are supported and their popularity has been rising among consumers worldwide. However, on the other hand, adequate rules are missing that would enable small and medium-sized companies to quickly market a sufficient spectrum of botanical pesticides, which would make it possible to intensify environmental production of plant products (Isman 2015).

In contrast, many various plant essential oils (e.g. clove, spearmint, citronella) have been approved as 'repellents'. However, there appears to be light at the end of the tunnel for individuals who want a more natural alternative to conventional insecticides in the European Union: at this time the European Food Safety Authority is looking at certain botanicals as 'low-risk active substances' (LRASs) or 'basic substances' as defined by (EC) Regulation No. 1107/2009. It should be noted that active ingredients should not be neurotoxic, immunotoxic, endocrine-disrupting, carcinogenic, mutagenic, corrosive or skin sensitisers (Marchand 2015). This ought to offer clarity and possibly a shorter regulatory channel for botanicals that meet these criteria (Chandler *et al*. 2011; Villaverde *et al*. 2014).

(III) ***The quality of BI formulations*** should be improved so that a sufficient persistence of their effect, quality and stability of the products are guaranteed. Some scientific sites are currently focused on this type of research. In an effort to increase biological efficacy, various so-called green syntheses of nanoparticles seem to be perspective, where the insecticidal efficacy of plant extracts is significantly enhanced (Benelli 2015a). In the past few years, micro- and nano-encapsulation procedures have been examined to see if they can provide a controlled release of botanical insecticides (Fang & Bhandari 2010; Chung *et al*. 2013). These technologies can prolong the efficiency of botanical insecticides over extended periods of time. Regardless of these formulation developments, the controlled release remained at the whole formula mixture level without calling for

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changes in the volatilisation and biological features of specific elements in the botanical materials used in the production of botanical insecticides. A better understanding about the behaviour and bioactivity of individual components of botanical insecticides in addition to new advanced methods of compartmentalisation and formulation is needed to allow us better degrees of control over the availability and activity of specific elements of intricate botanical mixtures. Therefore, this should help improve the efficiency of botanical insecticides (Chung *et al*. 2013; Miresmailli & Isman 2014).

CONCLUSION

Biopesticides, together with botanical insecticides, are more and more popular with food manufacturers and consumers equally. Many experts forecast a huge growth in the sales of botanicals over the next decade. Biopesticides could grow from 4–5% of the global pesticide market to as much as 20% by 2025. Growth in botanicals may perhaps be even higher, going from 1–2% of the market share to somewhere possibly around 7% of the total market share (Isman 2015).

The intensity of further research should also be adapted to this; at the minimum, the intensity should remain the same or be increased. It is also important to raise awareness among farmers who use farming products. In some areas in particular, high attention is now paid to raising awareness especially in developing countries where long-term projects are being designed and aimed at educating growers about the basic skills of manufacturing farming pesticides (Grzywacz *et al*. 2014).

The United States together with China have been the leaders in the commercialisation of botanical insecticides in the last few years, mainly due to regulatory schemes that encourage and facilitate the movement of 'reduced-risk' products on the market to get rid of older conventional insecticides which have less desirable properties. India, which has a solid track of recorded research on botanicals, has also approved a number of botanical insecticides, together with some that are not used elsewhere. The European Union still has the possibility of being an enormous market for botanical insecticides. However, it will be realised only if new criteria for 'low-risk active substances' facilitate regulatory approvals for newer and improved goods.

Although scientists keep coming up with new discoveries of promising insecticidal substances of plant origin (Isman & Grieneisen 2014), of which many may offer a commercial potential, numerous research results will remain only as a source of inspiration for subsequent generations without a suitable legislative background that would facilitate the marketing of products, especially those of small manufacturers.

Despite that, the BIs produced at present contribute at least partially to the minimisation of environmental and health problems associated with the application of some synthetic plant protection products.

Botanical insecticides should make headway by getting into a number of agricultural sectors particularly that of integrated pest management in high-value fruit and vegetable crops in addition to ectoparasite control in animals. Ever growing urbanisation should produce an expanding market with opportunities for botanical insecticides as human safety should also push the demand concerning professional pest control, consumer products as well as vector management.

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Received: 2016–02–29
Accepted after corrections: 2016–04–18
Published online: 2016–08–31

Corresponding author:

Ing. Roman Pavela, Ph.D., Výzkumný ústav rostlinné výroby, Drnovská 507, 161 06 Praha 6-Ruzyně, Česká republika; E-mail: pavela@vurv.cz