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Review

Comparing impacts of plant extracts and pure allelochemicals and implications for pest control

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Abstract

Many plant extracts or allelochemicals show a broad spectrum of activity against pests and such products have long been touted as attractive alternatives to synthetic chemical pesticides for pest management because they pose little threat to the environment or to human health. The studies available suggest that plant-based materials do affect arthropod pests, vectors and other pathogens, yet only a handful of botanicals are currently used in agriculture in the industrialized world, and there are few prospects for commercial development of new botanical products. Secondary allelochemicals from plants are usually commercialized as single, concentrated compounds, despite research showing that compound mixtures reduce pest resistance better than single compounds. Several factors appear to limit the success of botanicals, most notably regulatory barriers and the availability of competing products of microbial origin and fermentation products that are cost-effective and relatively safe compared with their predecessors. In the context of agricultural pest management, botanical pesticides are best suited for use in organic food production in industrialized countries but can play a much greater role in the production and post-harvest protection of food in developing countries. It is in developing countries that are rich in endemic plant biodiversity where these pesticides may ultimately have their greatest impact in future integrated pest management (IPM) programmes, given their safety to non-target organisms and the environment. However, there is a need to organize natural sources, develop quality control, adopt standardization strategies and modify regulatory mechanisms.

Keywords: Plant allelochemicals, Phytochemicals, Extracts, Essential oils, Biopesticides, Pest control, Commercialization

Introduction

The global population reached 6.705 billion in 2008 and is projected to increase to 9.352 billion in 2050. The population of developing countries will increase from 5.479 billion in 2008 to 8.058 billion in 2050. In contrast, the population in developed countries will increase from 1.227 billion in 2008 to 1.294 billion in 2050. In 2008, China occupied the first position with 1.325 billion people, followed by India with a population of 1.149 billion. However, by 2050, India would overtake China to occupy the first position with a population of 1.755 billion, with China predicted to have 1.437 billion people ([1], Figure 1). Such demographic changes would have profound implications for the economy, environment, health and quality of life of the people. Obviously, a huge population in the developing countries requires increased amounts of food and fibre from a shrinking agricultural land base. Intensification of agriculture through expansion of irrigation facilities, introduction of high-yielding varieties and application of increased amounts of agrochemicals has been in progress. In addition, cultural practices such as spacing, crop rotations, sowing times and tillage methods have been modified to achieve maximum productivity per unit time from the available land. However, along with various technological achievements, severe

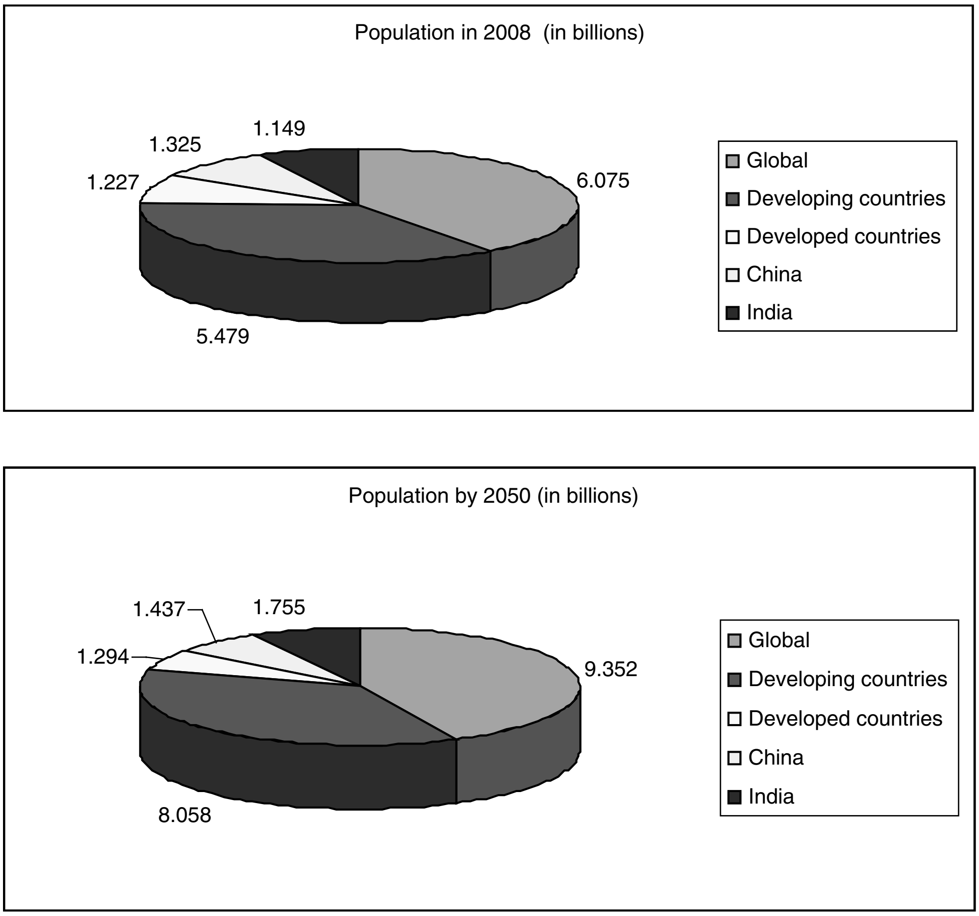


Figure 1 Human population in 2008 and projections for 2050

outbreaks of insect pests, diseases and weeds in agricultural crops have also occurred. Many hitherto-unknown species have assumed serious pest status and some of the serious pests have developed resistance to one or more groups of pesticides. In addition, pesticides have contaminated different components of our environment and pose a potential health hazard to consumers. Therefore, future pest problems will have to be tackled in an environmentally benign manner as a part of a sustainable crop production technology [2–4].

Pest management should be ecologically based (EBIPM) and should be undertaken within the context of integrated crop management (ICM) and integrated pest management (IPM) and the best option is to use eco-friendly approaches. In fact, the use of biopesticides, specifically plant-based products, has gained a lot of importance, particularly chemicals/secondary metabolites from a plant that affect the pests through negative effects. Plant biodiversity has provided an excellent source of biologically active materials for use in traditional crop protection. Plant-based products have been used as extracts, the essential oils or pure allelochemicals. In general terminology, the extracts are concentrated mixture preparations of plant parts obtained from a suitable solvent, which is evaporated away, and the residue is then adjusted to a prescribed standard. Essential oils, in contrast, are fragrant oils from aromatic plants, which are widespread all over the world, although 49% of them belong to the families of Lamiaceae and Compositae in regions with Mediterranean-type climate [5], and contain mixtures of low molecular weight (hence volatile) isoprenoid compounds secreted and stored in specialized tissues (trichomes, cavities, ducts, canals, etc.). Allelochemicals are secondary metabolites or non-nutritional primary metabolites, which could be the components of both extracts or essential oils, that affect growth, reproduction or behaviour of individuals other than the ones producing them, or structure and dynamics of populations or communities of either plants or animals or microbes [6]. The scope of allelochemicals is far wider than that associated with allelopathy and covers a variety of interactions mediated by chemicals with the above properties.

Although noted for the complexity of their chemical structures and biosynthetic pathways, allelochemicals have been investigated for their chemical properties extensively since the 1850s. Recognition of the biological properties of large number of phytochemicals has fuelled the current focus on the search for new drugs, antibiotics, insecticides, herbicides and behaviour-modifying chemicals. Many of these compounds have been shown to have important adaptive significance in protection against herbivory [7]; in fact, phytochemical diversity of insect defences in tropical and temperate plant families has been significantly established [8]. Most of the compounds have been established as insect antifeedants [9]. Although allelochemicals mediate a wide variety of complex interactions, allomonal chemicals fall into one of the two basic categories. The first of these include materials produced by the organisms and released into the environment, mostly volatile compounds, which exert their influence over some distance from the emitter. Such volatiles include a wide variety of short-chain alcohols and aldehydes, ketones, esters, aromatic phenols, mono- and sesquiterpenes and a host of other secondary metabolites. The second group of allomones includes compounds produced or acquired for defence, which remain in the body of the producer. This group includes toxins sequestered by insects for defence and the vast array of phytochemicals. In fact, in recent decades, literature has been flooded with umpteen studies where extracts, isolated compounds or combination products have been evaluated for their efficacy against a variety of pests. These studies have been comprehensively reviewed [8–25]. Recently, interests in the essential oil allelochemicals were also renewed with emerging demonstration of their fumigant and contact insecticidal activities to a wide range of pests [26–28]. However, the objective of the present review is to compare impacts of plant extracts and pure allelochemicals and to discuss their implications for pest control.

Plant Products and Allelochemicals for Pest Control

The use of plants as pesticides has been practiced since time immemorial. For thousands of years, people in India placed neem leaves in their beds, books, grain bins, cupboards and closets. The Hindu book, the *Rig Veda,* written in India in 2000 BC, makes a mention of the use of poisonous plants for pest control. It is quite probable that the exploitation of the toxicological properties of plants has an even older history. Prior to the onset of agriculture, local people had already deified trees and many plant-based extracts were believed to possess special powers, particularly for healing. With the development of agriculture, links would have rapidly been made between food production and pest control. These links might have provided an opportunity for this specialized knowledge to be used directly for protection of crops against pests [29].

Plants are biochemists *par excellence*. During their long evolution, plants have synthesized a diverse array of chemicals to prevent their colonization by insects and other herbivores. Only about 10% of these have been examined chemically, indicating that there is enormous scope for further work [30]. Over the years, more than 6000 species of plants have been screened and more than 2500 plant species belonging to 235 families [31] possessed biological activity against various categories of pests. This number seems to be far less than the actual number of naturally occurring pesticidal plants, as it constitutes just 0.77% of the total 308 000 species of plants or 0.87% of 275 000 species of flowering plants [32]. It is thus likely that novel and potent molecules that can be used for pest suppression still remain to be discovered from many plant species. In fact, in-built defence systems in plants can be visualized through several factors. Some leaf exudates are toxic to insects. Leaf glandular trichomes and the exudates such as cuticular waxes produced by them play a significant role in determining resistance and susceptibility to infestation by insects in these plants [33, 34]. These exudates produce a microcrystalline layer of waxy material, comprising of a number of secondary plant metabolites such as glycolipids, glycerolipids as well as free fatty acids/esters and terpenes. These materials, besides providing in-built plant resistance to invading pests, are active against certain phytophagous insects and pathogens. For some of the insects, the presence of a high level of long-chain alcohols such as 1-hexacosanol (C26) in cabbage wax and 1-triacontanol (C30) in alfalfa (lucerne) have been associated with resistance to larvae of the diamondback moth, *Plutella xylostella*.

High levels of α-amaryl alkanoates and cycloartenyl alkanoates in epicuticular waxes in plants act as defence systems against insects. Abundance of cycloartenol alkanoates in raspberry (*Rubus idaeus*) is considered as significant factor in resistance against *Amphorophora idaei.* Interestingly, aphid-derived triacylglycerol, found only in the leaf waxes of aphid-infested plants, serves as an index of aphid infestation [33, 34]. Antixenotic resistance of various *Brassica* species to turnip rootfly, *Delia floralis*, has also been linked to the presence of wax esters [33, 34]. Glycerolipids in combination with glycolipids such as glucose and sucrose esters make *Nicotiana benthamiana* resistant to attack by the hornworm, *Manduca sexta* [35]. In addition, there are a number of secondary metabolites that provide defence to plants against pests. Therefore, a general approach has been to use botanical products against pests in the form of various extracts containing a group of active ingredients of diverse chemical nature or the isolated allelochemicals, which induce various types of inhibitions in the developmental processes of pests.

Insect Control

Several extracts of plants have been evaluated for their activity against agriculturally important insects for a few decades now [15, 36–45] and are currently being evaluated further for use in plant protection because of their possible ecofriendly characteristics. Some very recent studies also clearly demonstrate the efficacy of a number of such extracts. For instance, contact and residual toxicity of more than 30 plant extracts were investigated on larvae of Colorado beetle [46], where results exhibited that certain plant extracts were toxic to the beetle larvae and may have potential for controlling this destructive pest under field conditions [47]. The behavioural and electrophysiological responses of the obliquebanded leafroller to crude extracts of plant extracts do reveal the inhibition of oviposition [48]. Some plant extracts are also toxic to aphids [49] and generalistic lepidopterans [50]. Antifeedant and larvicidal activity of acetone, chloroform, ethyl acetate, hexane and methanol peel, leaf and flower extracts of *Citrus sinensis*, *Ocimum canum*, *Ocimum sanctum* and *Rhinacanthus nasutus* against lepidopterans suggest their potential as an ideal ecofriendly approach for the control of the agricultural pests [51]. On the African continent, several plant extracts of African plant species such as *Pseudocedrela kotschyi*, *Strophanthus hispidus*, *Securidaca longepedunculata*, *Sapium grahamii*, *Swartzia madagascariensis*, *Cassia nigricans*, *Jatropha curcas*, *Datura inoxia* and *Piper guineense* [52, 53] have potential to control lepidopteran pests and white flies.

There is substantial work available where plant extracts have been evaluated against mosquitoes [51, 54, 55]. These extracts exhibit combined effects on the developmental period and adult emergence, which occasionally extend to the progeny of exposed larvae. Plant-based products produce morphological abnormalities in different developmental stages of mosquitoes, such as abnormal melanization in larval and pupal stages, larval–pupal intermediates, or abnormal ecdysis, which suggests a metamorphosis-inhibiting effect of the plant extract through disturbance of the hormonal milieu during the moulting process [56–63]. Plant extracts could also significantly control vectors. This is obvious from the studies on Chagas' disease vector, which is chiefly transmitted by faeces of haematophagous bugs (Triatominae) that ingest *Trypanosoma cruzi* from blood of infected people or animals. Insecticidal activity of 24 cerrado plant extracts belonging to five species of four families were assayed on fourth instar nymphs of *Rhodnius milesi* (Hemiptera: Reduviidae), under laboratory conditions. For the extract application of triatomines, 50 μg of the extract were topically applied. Triatomines were observed over a 28-day period. Hexanic and ethanolic extracts of *Simarouba versicolor*, *Guarea kunthiana*, *Guarea guidonia* and *Talauma ovata* caused mortality of 20–95% of *R. milesi*. This suggests that such extracts could be exploited further as molecular models or as biorational compounds for use in vector control programmes [64].

There are also several examples of essential oils such as those of lemongrass (*Cymbopogon winterianus*), *Eucalyptus globulus*, rosemary (*Rosmarinus officinalis*), vetiver (*Vetiveria zizanioides*), clove (*Eugenia caryophyllus*) and thyme (*Thymus vulgaris*) that are known for their pest control properties. While peppermint (*Mentha piperita*) repels ants, flies, lice and moths; pennyroyal (*Mentha pulegium*) wards off fleas, ants, lice, mosquitoes, ticks and moths. Spearmint (*Mentha spicata*) and basil (*Ocimum basilicum*) are also effective in warding off flies. Insecticidal effects of essential oils extracted from 11 Greek aromatic plants on *Drosophila auraria* are well known [65]. Several Mediterranean plants are rich in essential oils and insecticidal to bruchids [66–69]. Similarly, essential-oil bearing plants such as *Artemisia vulgaris*, *Melaleuca leucadendra*, *Pelargonium roseum*, *Lavandula angustifolia*, *M. piperita* and *Juniperus virginiana* are also effective against various insects and fungal pathogens [70]. Volatile oil of *Mentha* species or plant extracts and *S. longepedunculata* do inhibit the development of stored grain pests [71–73]. Essential oil from *Cinnamomum zeylanicum*, *Cymbopogon citratus*, *L. angustifolia* syn. *Lavandula officinalis*, *Tanacetum vulgare*, *Rabdosia melissoides*, *Acorus calamus*, *Eugenia caryophyllata*, *Ocimum* spp., *Gaultheria procumbens*, *Cuminum cyminum*, *Bunium persicum*, *Trachyspermum ammi*, *Foeniculum vulgare*, *Abelmoschus moschatus*, *Cedrus* spp. and *Piper* species are also known for their varied pest control properties [28].

Citronella (*Cymbopogon nardus*) essential oil has been used for over 50 years both as an insect repellent and an animal repellent. Combining a few drops each of citronella, lemon (*Citrus limon*), rose (*Rosa damascena*), lavender and basil essential oils with one litre of distilled water is effective as a means of warding off indoor insect pests. The larvicidal activity of citronella oil has been mainly attributed to its major monoterpenic constituent citronellal [74]. Vetiver (*V. zizanioides*) essential oil obtained by steam distillation of aromatic roots contains a large number of oxygenated sesquiterpenes. This oil is known to protect clothes and other valuable materials from insect attack when placed in closets, drawers and chests.

Many other plant essential oils, like those from *O. sanctum* [75], *Satureja hortensis*, *Thymus serpyllum* and *Origanum creticum* [76], *Ageratum conyzoides* [77] and *Aegle marmelos* and *Lippia alba* [78] are either toxic or growth inhibitory against *Spodoptera litura* larvae.

On the whole, it is apparent that many essential oils as mixtures have the potential to control a variety of insect pests, particularly as fumigants given their volatile nature, though some studies indicate their potential against agricultural pests, if suitable delivery systems are developed for their judicious use.

In addition to the above-mentioned extracts or essential oils from plants, many insecticidal compounds have been isolated and evaluated against many insect species. Among traditional botanical biopesticides, commercial use began in the nineteenth century with the introduction of nicotine from *Nicotiana tabacum*, rotenone from *Lonchocarpus* sp., derris dust from *Derris elliptica* and pyrethrum from *Chrysanthemum cinerariifolium*. Rotenones, the first-generation botanical pesticides, have been extensively used in the past to control household and agricultural pests. Their use, however, had to be dispensed with because of high fish and/or mammalian toxicity. Nicotine, an alkaloid obtained from *N. tabacum*, *Nicotiana rustica* and *Nicotiana glutinosa* is another well-established botanical insecticide. Nicotine analogues such as nor-nicotine and anabasine also possess insecticidal properties. Nicotine is active against piercing–sucking insects such as aphids, leafhoppers, whiteflies, thrips and mites [79]. However, because of high mammalian toxicity and detrimental effects on human health, its use as an insecticide has decreased considerably.

Sabadilla alkaloid derived from sabadilla (*Schoenocaulon officinale*) and a number of *Veratrum* species, generally referred to as *Veratrum* alkaloids are also known for their insect control properties. The insecticidal activity of sabadilla comes from the alkaloid fraction, which constitutes 3–6% of the extract. The two most important lipophilic alkaloids in the extract have been identified as veratridine and cevadine, the former being more insecticidal. The major effects of sabadilla poisoning include muscle rigour in mammals and paralysis in insects. Its mode of action is similar to that of the pyrethroids and it acts through disruption of nerve cell membranes, causing loss of nerve function, an increase in the duration of the action potential, repetitive firing, and a depolarization of the nerve membrane potential owing to effects on the sodium channel. Sabadilla alkaloids are labile and break down rapidly in sunlight. These are less toxic to mammals than most other insecticides and are therefore safe to use.

Pyrethrum, the most widely used botanical insecticide is extracted from the flowers of *Tanacetum* (*Chrysanthemum*) *cinerariifolium* (pyrethrum). It is highly effective against houseflies, mosquitoes, fleas and lice. The toxins, namely pyrethrins, cinerins and jasmolins, have some unusual insecticidal properties, most striking being the immediate knockdown or paralysis on contact, which causes most flying insects to drop almost immediately upon exposure [80]. These compounds act both on the central nervous system and in the peripheral nervous system causing repetitive discharges, followed by convulsions. Pyrethrins have low toxicity to vertebrates and have found wide acceptance worldwide. As with most other natural pesticides, pyrethrins are labile, they have limited stability under field conditions and are rapidly degraded by sunlight and heat. These are generally formulated with synergists such as piperonyl butoxide (PBO) to inhibit detoxification and improve insect mortality. Natural pyrethrins are considered as the best example of products manipulated in the laboratory to discover a highly effective group of insecticides (the synthetic pyrethroids).

Thus successful use of traditional botanicals has aroused further interest in exploring plant biodiversity for new bioactive phytochemicals and extractives as a possible source of pest control agents. Some of the recent developments are described below.

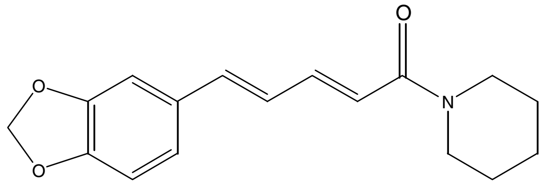
Isobutylamides

A large number of unsaturated isobutylamides have been isolated from various species of genus *Piper* (Piperaceae), which are known to have diverse insecticidal actions. The compounds have been isolated from the fruits, stem and leaves of various *Piper* species such as *Piper nigrum*, *Piper acutisleginum, Piper khasiana, Piper longum, Piper pedicellosum* and *Piper thomsonii* [14]. Screening of other species in the genus points to numerous other potential sources of natural insecticides, such as *Piper retrofractum* from Thailand, *P. guineense* from West Africa and *Piper tuberculatum* from Central America [81]. Some of the active compounds include piperlonguminine, piperine, pipericide, dihydropipericide and pellitorine. Recently, pellitorine (Figure 2) and 4,5-dihydropiperlonguminine were extracted from the seeds of *P. tuberculatum* (Piperaceae) in yields of 6.10 and 4.45%, respectively. The acute toxicities to the velvetbean caterpillar, *Anticarsia gemmatalis*, of these compounds were determined. The LD_{50} and LD_{90} values were 31.3 and 104.5 μg/insect, respectively for pellitorine and 122.3 and 381.0 μg/insect for 4,5-dihydropiperlonguminine [82]. This suggests that these amides have substantial potential in IPM. All the unsaturated isobutylamides are neurotoxins that impair or block voltage-dependent sodium channels on nerve axons. Being neurotoxic, these amides show both knockdown and lethal action against pyrethroid susceptible and resistant insects. They are extremely unstable molecules, but are toxic to a range of insect pests. The information on their environmental or mammalian toxicity is scanty, primarily because they are not yet commercially available.

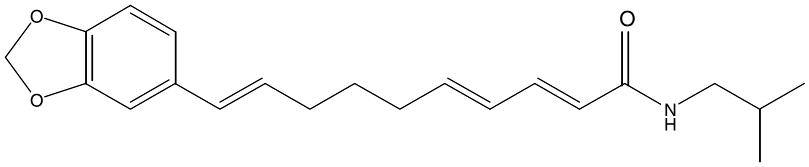
According to Scott *et al.* [83] the piperamides found in *Piper* species are bifunctional, as an isobutyl amide functionality is combined with a methylenedioxyphenyl (MDP) moiety. In addition, the piperamides present dual biological activities, being neurotoxic and also inhibitors of cytochrome P450 enzymes. These characteristics are useful to plants of *Piper* genus as a defence strategy against herbivores. *Piper* extracts, as with other insecticides, can be hazardous unless the applicator takes precautions, for *Piper* active components are known irritants. Fortunately, the risk to human health is much reduced because the active components have had a safe history as food additives and spices [83]. However, care must be taken to prevent such products from reaching non-target organisms, such as beneficial insects. Miranda *et al.* [84] evaluated the susceptibility of *Apis mellifera* to pellitorine and found LD_{10} values of 39.1 ng AI/larva and if LD_{50} of pellitorine is compared with the velvetbean caterpillar (31.3 μg/insect), a value that is 1000 times higher than the LD_{10} for honeybee larvae. Thus, the honeybee larvae were shown to be highly susceptible to pellitorine. Additionally, further evaluation of the effects of piperamides on other non-target organisms, such as the pests' natural enemies, should be carried out.

Limonoids and Quassinoids

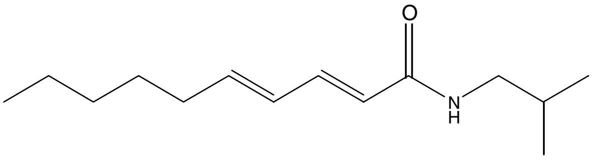
Two major groups of metabolically altered triterpenes, the limonoids (tetranortriterpenoids) and the quassinoids



Piperine



Pipericide



Pellitorine

Figure 2 Examples of insecticidal isobutylamides

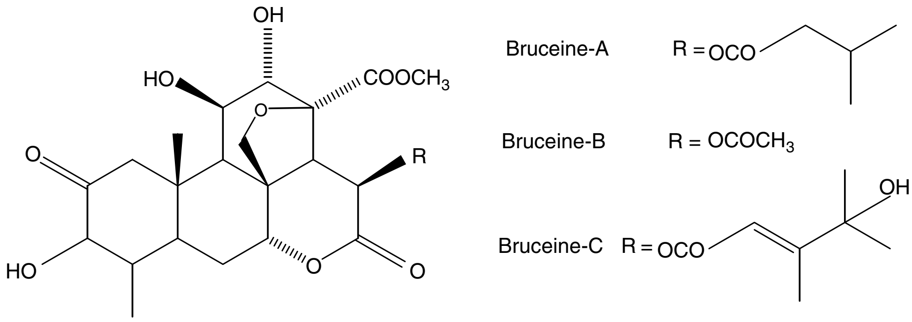
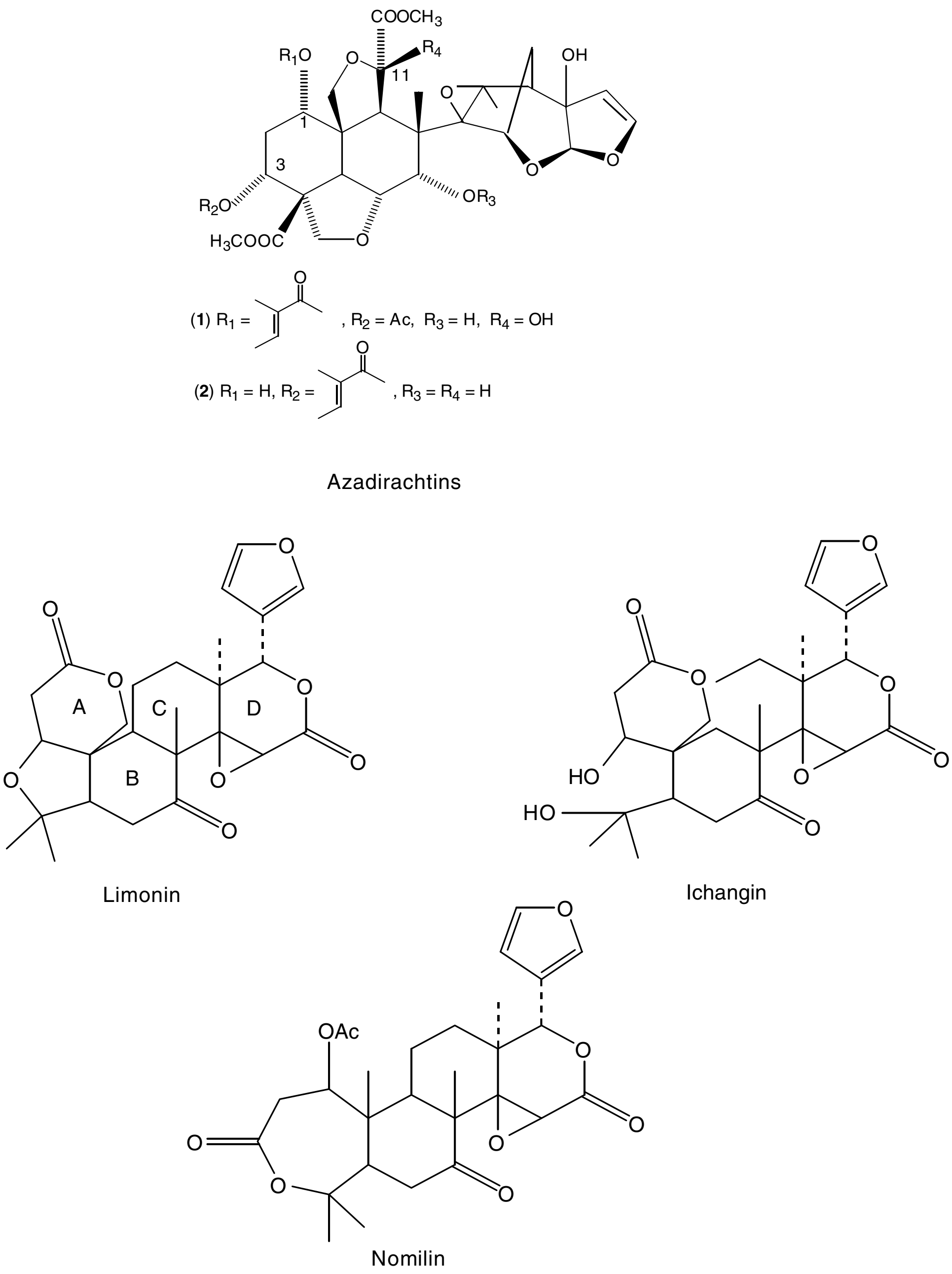


Figure 3 Some active bruceine type of quassinoids

(decanortriterpenoids) are derived from the triterpenoid precursor euphol. These compounds are limited in distribution to the families Rutaceae, Meliaceae, Cneoraceae, Simaroubaceae, and perhaps the Burseraceae. These compounds presumably arise from mevalonic acid pathways as the triterpenoid precursor euphol is a key intermediate in their biosynthesis. Both groups of compounds are derived from condensation of a chair–chair–chair–boat configured squalene epoxide precursor. Most of the intermediates and enzymes in these pathways remain unstudied. Euphol appears to be the precursor of most of these compounds, although another compound tirucallol (with opposite configuration at C20) may be involved in the formation of some compounds. Δ^7-euphol and/or Δ^7-tirucallol appear to be the later intermediates in the pathway. Apo-euphol and apo-tirucallol, C30 compounds or protolimonoids, have features that also suggest that they are intermediates. There are at least 300 known members of this group of compounds. They are stereochemically homogeneous. Oxidative modification results in the removal of the four-terminal side-chain carbons and formation of a β-substituted furan ring. Various classes of limonoids have the A, B, C or D ring (or some combination of them) cleaved. For example, limonin has a cleaved A ring and a D ring and is an A,D-*seco*-limonoid (Figure 4). The initial products of the oxidation process are concealed by secondary cyclization.

Quassinoids occur only in the family Simaroubaceae. More than 120 compounds of this type have been described. The biosynthetic precursors of this series are



Azadirachtins

Limonin

Ichangin

Nomilin

Figure 4 Examples of active limonoids

similar to those of limonoids. Δ^7-euphol and/or Δ^7-tirucallol appear to be involved. After a series of reactions, cleavage of the C_{13}–C_{17}-bond leads to the formation of C-20 quassinoids. Inadequate data exist to define clearly the pathway of biosynthesis. Quassinoids, which are more like limonoids rather than degraded triterpenes, also possess anti-insect properties. Compounds such as bruceantin, bruceine-A, bruceine-B, bruceine-C (Figure 3) and bruceine-D from *Brucea antidysenterica* are antifeedant compounds for tobacco budworms, Mexican bean beetles and southern armyworms [9]. These compounds with A-ring enerone function induce potential feeding deterrence to these insects.

Among limonoids, the best known compound is azadirachtin (Figure 4) from *Azadirachta indica* [4, 17, 85–87]. This compound is active against a broad spectrum of insects and is a known potential insecticidal antifeedant and insect growth regulatory allelochemical from neem [86–88]. Other limonoids from the same plant or in rutales, in general, have many activities against insect pests [12]. A similar series of compounds is found in a related plant, *Melia azedarach*. The fruits of this species are quite toxic to livestock as well. These compounds, such as toosandanin and meliatoxins, have been recorded as having potential for pest control [89, 90].

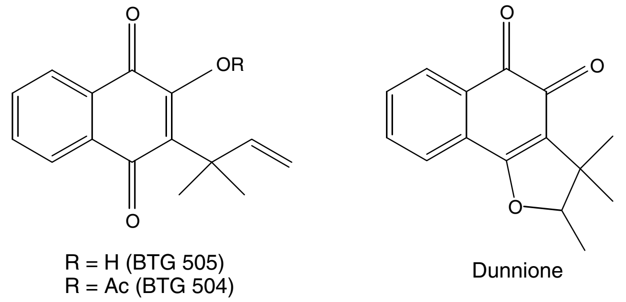


Figure 5 Examples of insecticidal natural naphthaquinones

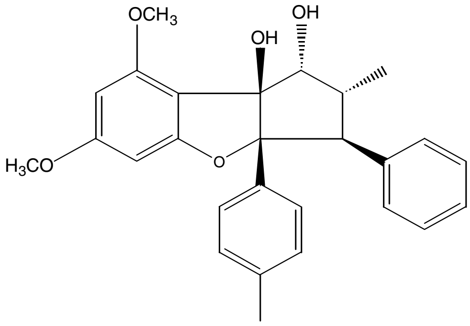
In a number of citrus species, the bitterness causative factors are limonoids, limonin (Figure 4) being one of the potential antipest compounds known. A few other citrus limonoids, including nomilin, nomilinic acid, ichangin and obacunoic acid are also bitter. Among these, limonin and nomilin (Figure 4) are known to deter feeding in lepidopterans and coleopterans with variable efficacies [12]. It appears that furan and epoxide groups have to play a major role in the activity of these compounds. A possible role of C-7 is implied by the modest activity of the 7-hydroxylated de-epoxy system [91]. For instance, highly reduced activity of deoxyepilimonol against limonin demonstrates the above conclusion. In certain cases, the cyclohexenone A ring and the α-hydroxy enone group in the B ring appear to be important for antifeedant activity. Also, the absence of 14–45 epoxide may not drastically reduce antifeedant activity [92]. Some structural activity relationships have also been drawn by preparing some semisynthetic derivatives of citrus limonoids, suggesting the potential of functional groups for the activity [93].

Napthoquinones

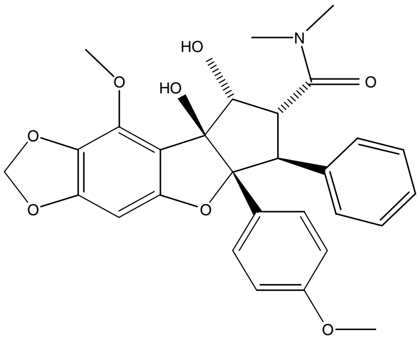
The biological activity of 2-hydoxy-3-substituted-1,4-naphthoquinones was first reported by Fieser *et al.* [94]. Lapachol obtained from the wood extract of *Tabebuia serratifolia* (Bignoniaceae) is antifungal [95] and shown to be more active (LC_{50}=20.8 ppm) than the amine derivatives (LC_{50}=242.6–899.4 ppm) when obtained from an ethanolic bark extract of *T. serratifolia* against the larvae of *Aedes aegypti* [96]. Two active principles from the Chilean plant *Calceolaria andina* (Scrophulariaceae), related to the familiar garden 'slipper' plant, have been identified as hydroxynapthoquinone and its acetate, designated as BTG 505 and BTG 504 (Figure 5), which are effective against a range of commercially important pests including the tobacco whitefly, *Bemisia tabaci*, aphids and the two-spotted spider mite, *Tetranychus urticae* [97]. They offer opportunities both as lead structures for analogue synthesis [98] and as new botanical pesticides [99] exhibiting low mammalian toxicity unlike other naphthoquinones. The use of these compounds as pesticides has been patented [97] by BTG International Ltd. The primary mode of action in insects is by inhibition of complex III of the mitochondrial respiratory chain [100]. The insecticidal and fungicidal properties of dunnione (a known naphthoquinone, Figure 5) have been compared with natural BTG 505 [101]. Although dunnione showed practically no activity against the house fly *Musca domestica*, the whitefly *B. tabaci*, the beetle *Phaedon cochleariae*, or the spider mite, *T. urticae*, unlike BTG 504 and BTG 505, dunnione had an unusually broad spectrum of antifungal activity. The mode of action of dunnione is primarily through initiation of redox cycling, whereas BTG 505 acts by inhibiting mitochondrial complex III [101].

Rocaglamides

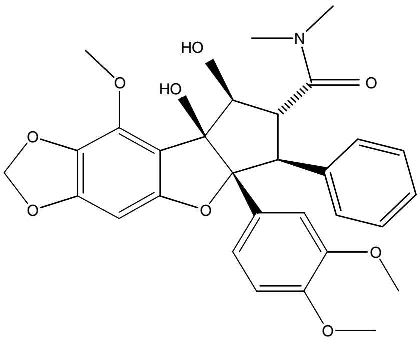
These are the class of compounds mostly found in genus *Aglaia*. An outstanding property of these compounds is that they are effective against a range of resistant insect strains including the notorious B-biotype of the tobacco whitefly, *B. tabaci*, which is devastating crops worldwide. The genus *Aglaia* consisting of some 130 species widely distributed in the Indo-Malaysian region [102] has attracted considerable attention in the past decade as a possible source of unique natural products. Phytochemical investigations of *Aglaia* have revealed the presence of a variety of compounds, including rocaglamides [103, 104], aglains [105], bisamides [106], triterpenes [107] and lignans [108], with interesting biological activities. There are more than 50 naturally occurring rocaglamide derivatives isolated to date (e.g., rocaglamide, Figure 6) [104]. Rocaglamide derivatives are unusual aromatic compounds, featuring a cyclopentatetrahydrobenzofuran skeleton and are strictly confined to members of *Aglaia*. Recently, several novel rocaglamide derivatives isolated from different *Aglaia* species have been shown to have strong insecticidal activity (in some cases even comparable to azadirachtin), mostly against neonate larvae of *Spodoptera littoralis*, *Ostrinia* species and the gram pod borer, *Helicoverpa armigera* [3, 102, 106, 109–113]. The insecticidal mode-of-action as well as the potential anti-cancer activity of rocaglamides results from inhibition of protein synthesis, explaining the long time-to-death in treated insects [114]. The insecticidal activity of rocaglamides can be attributed to the presence of the furan ring system, since the closely related aglains, possessing a pyran ring, are devoid of insecticidal activity [102]. The nature of the substituents at C1, C2, C3 and C8 has also been suggested to be responsible for the bioactivity of the respective derivatives [102, 109, 115]. Acylation of the OH group (with formic or acetic acid) at C1 caused a reduction of insecticidal activity in neonate larvae of *S. littoralis* compared with other rocaglamide derivatives with a hydroxyl substituent isolated from the twigs of *Aglaia duperreana* [109]. The reduction of insecticidal activity in the acetylated derivative indicates the first



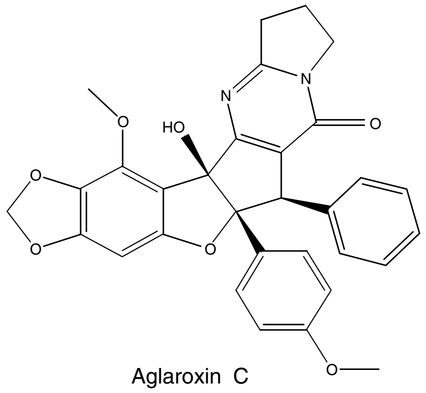
Rocaglamide



Aglaroxin A



Aglaroxin B



Aglaroxin C

Figure 6 Aglaroxins and rocaglamide from *Aglaia elaeagnoidea*

structure–activity relationship in this group of natural insecticides. There is a decline in insecticidal activity for rocaglamide derivatives featuring an unsubstituted C2 in contrast with analogues possessing an amide or carboxylic substituent at this position. A similar trend has been noted in other rocaglamide derivatives isolated from *Aglaia odorata* [102, 111] and *Aglaia elliptica* [110]. Substitution of a hydroxy group with the methoxy group at C8b resulted in a complete loss of activity in compounds that were isolated from roots of *A. duperreana* [116] showing the importance of the OH group at C8b. The strong bioactivity of rocaglamide derivatives against a number of insect pests suggests that they may serve as lead structures in the development of natural insecticides for plant protection. Among the various botanicals isolated from *A. odorata, A. elliptica* and *A. duppereana* (Meliaceae), rocaglamide is the most effective (EC_{50}= 0.8 ppm). It is slightly more potent than azadirachtin (EC_{50}=1.0 ppm) against some insect species [117]. As growth inhibitors, rocaglamide and methyl rocaglate are similar in their activity (EC_{50}=0.9 ppm) and quite comparable to azadirachtin (0.26 ppm) [118], as are the aglaroxins isolated from other *Aglaia* species [119, 120]; Figure 6.

Sesquiterpenes and Sesquiterpene Polyol Esters

Sesquiterpenes are an important source of insect antifeedants [121]. Several insecticidal and antifeedant sesquiterpenoids are known as major deterrents in insect–plant interactions [122–129]. Tricyclic silphinene, a sesquiterpene namely 11β-acetoxy-5α-(angelyloxy)-silphinen-3-one and two of its hydrolytic products 11β-hydroxy-5α-(angeloyloxy)-silphenen-3-one and 11β,5-dihydroxy silphinen-3-one reported from *Senecio palmensis* (Asteraceae) are strong antifeedant compounds against the Colorado potato beetle, *Leptinotarsa decemlineata* (Say) [130]. Two compounds have been isolated from *S. palmensis*, one from the chemical class of bisabolenes and the other from a silphinene sesquiterpene [131]. Both chemicals may alter the host selection process through adult behavioural avoidance because adults are highly mobile and are the primary finders of host plants [121]. Siliphene sesquiterpenes, however, have both antifeedant and toxic effects against insects.

Some feeding deterrents such as sesquiterepene lactone angelate argophyllin-A and 3-O-methyl niveusin-A have been isolated from inflorescences of cultivated sunflower. α-Cyperone, a sesquiterpene isolated from the *Cyperus rotundus* (nutgrass) tubers is insecticidal against diamondback moth *P. xylostella* [132]. Drimane group of sesquiterpenes occur in the marsh pepper *Polygonum hydropiper* (Poligonaceae), besides in the plants of the genera *Warburgia*, *Cinnamosma*, *Winterana* and *Cinnamodendron* (Cannellaceae). Such compounds reportedly possess a broad spectrum of activity. Poligodial, warburganal and muzigadial are among some of the potential drimane sesquiterpenes having anti-insect and antifungal properties [133]. Inhibition of feeding in monophagous as well as polyphagous insects has been attributed to enal and α,β-unsaturated aldehyde group(s) in these molecules [134]. The biological activity is primarily the result of their ability to form adducts with amino groups rather than sulphydryl group of the receptors [135]. Kauranoid alcohols have been reported from the important medicinal plant *Croton lacciferus* commonly found in Sri Lanka and India [136]. These compounds are moderately insecticidal against *Aphis craccivora* [137]. Costunolide and parthenolide, the two bioactive sesquiterpene lactones isolated from the fruits of *Magnolia salicifolia*, are toxic to *A. aegypti*, inducing absolute mortality within 24 h at 15 ppm [138].

The root bark of Chinese bittersweet *Celastrus angulatus* is traditionally used in China to protect plants from insect damage and contains polyol ester celangulin that deters feeding in insects. This compound has a dihydroagarofuran skeleton with seven hydroxyl functions, five of which are acylated, one benzoylated and one free [139]. Other compounds of similar skeleton like wilfordine from *Tripterygium wilfordii* [140] and wilforine from *Maytenus rigida* are also known insect antifeedants [141]. This suggests that dihydroagarofuran skeleton plays a significant role in the feeding deterrent activity. This is supported by the efficacy shown by similar class of compounds isolated from seed oil of *Euonymus bungeanus* [142]. The antifeedant and insecticidal activity of these polyol esters against *Pieris rapae* and *Ostrinia furnacalis* have been attributed to the ester moieties attached to the decalin portion of the molecule. A number of such compounds have been comprehensively discussed [9, 13]. Some recent records also show such terpenes isolated recently from Rutales are effective antifeedants for stored grain pests, particularly the spirocaracolitones, which are absolute antifeedants [21].

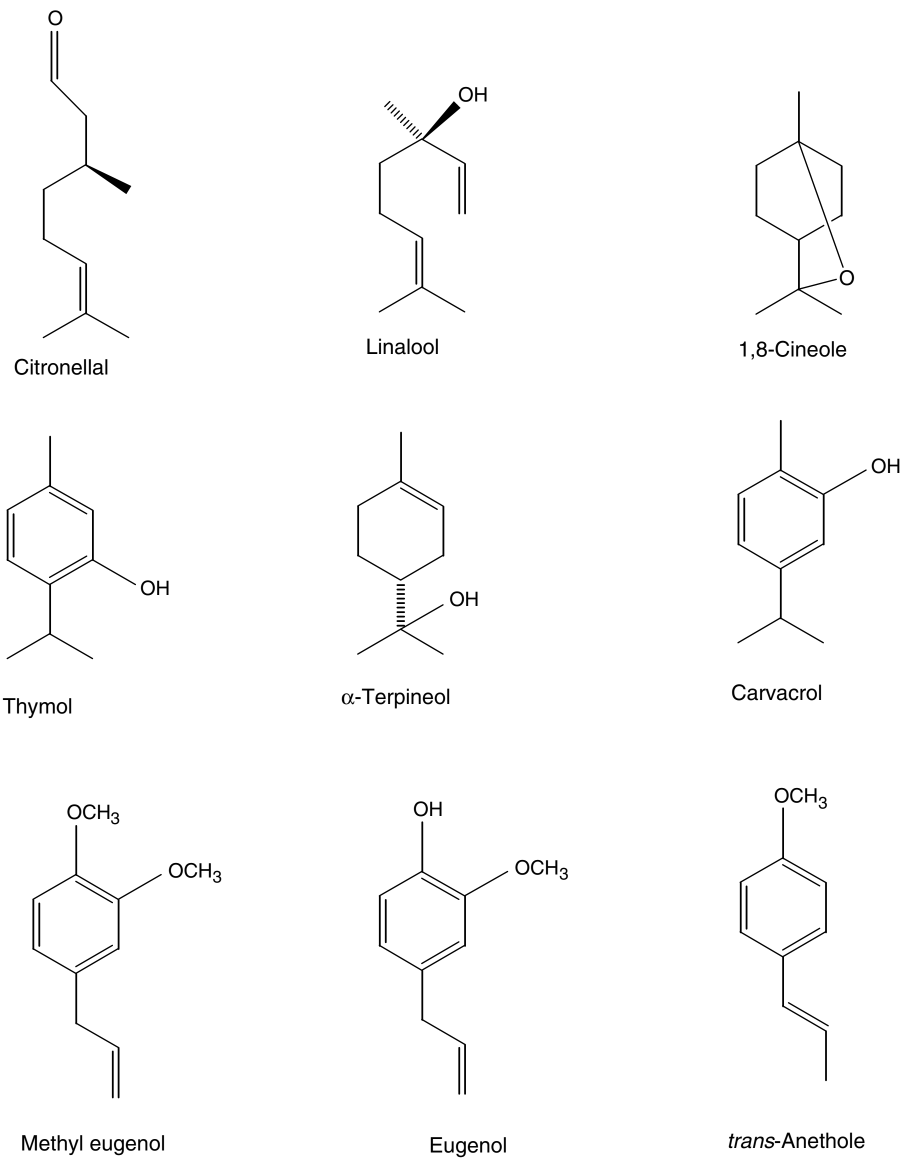
Monoterpenes

Many monoterpenes (Figure 7) from plant sources have been evaluated as feeding deterrents against insects [28, 143] and are complex mixtures of natural organic compounds of plant essential oils that are predominantly composed of terpenes (hydrocarbons) such as myrecene, pinene, terpinene, limonene, *p*-cymene, α- and β-phellandrene; and terpenoids (oxygen containing hydrocarbons) such as acyclic monoterpene alcohols (geraniol and linalool), monocyclic alcohols (menthol, 4-carvomenthenol, terpineol, carveol and borneol), aliphatic aldehydes (citral, citronellal and perillaldehyde), aromatic phenols (carvacrol, thymol, safrole and eugenol), bicyclic alcohol (verbenol), monocyclic ketones (menthone, pulegone and carvone), bicyclic monoterpenic ketones (thujone, verbenone and fenchone), acids (citronellic acid and cinnamic acid) and esters (linalyl acetate). Some essential oils may also contain oxides (1,8-cineole), sulphur-containing constituents, methyl anthranilate, coumarins, etc. Zingiberene, curcumene, farnesol, sesquiphellandrene, termerone, nerolidol, etc. are examples of sesquiterpenes (C15) isolated from essential oils. Phenolics from plants are also a good source of bioactive compounds [144]. Many monoterpenes possess potent biological activity against pests and have been commercially exploited during the past decade and some have been commercialized by EcoSmart in the USA. These studies have been comprehensively reviewed recently by us [28], therefore, not included here.

Clerodane Diterpenes

Neo-clerodane diterpenes are a promising group of compounds that affect the feeding behaviour of insect pests. Approximately 150 neo-clerodanes have been isolated [145, 146] and among these, eriocephalin and teucvin are quite effective along with ajugarins isolated from *Ajuga remota* [147–149]. Compounds resembling ajugarins such as ajugareptansin and ajuga reptanoside-A and -B from *Ajuga reptans* [150] and *Ajuga riva* [151] are also significant anti-insect allelochemicals.

Neo-clerodane diterpenoids isolated from various species of *Teucridium*, *Ajuga* and *Scutellaria* (Family Lamiaceae) also inhibit feeding in lepidopteran larvae. From the aerial parts of *Scutellaria galericulata*, jodrellin-T, 14,15-dihydro jodrellin-T and galericulin are novel structures [9]. Jodrellin-B, also reported from *Scutellaria woronowii,* is the most active compound in this series and Scutalpin-C



Citronellal Linalool 1,8-Cineole

Thymol α-Terpineol Carvacrol

Methyl eugenol Eugenol *trans*-Anethole

Figure 7 Insecticidal compounds from essential oils

from *Scutellaria alpina javalaambrensis* was very active against *S. littoralis* [152]. It has been shown that saturation of the dihydrofuran ring and addition of the tigloyl ester function at C-1 results in decreased activity [153, 154]. Both clerodane and neoclerodane group of diterpenoids are well known for their insecticidal [155] and antifeedant activity [154, 156].

Clerodane diterpenes, 3,13*E*-clerodane-15-oic acid, 4,13*E*-clerodane-15-oic acid, 18-oxo-3,13*E*-clerodane-15-oic acid and 2-oxo-3,13*E*-clerodane-15-oic acid from the Nigerian plant *Detarium microcarpum* are feeding deterrents [157], particularly against workers of the subterranean termite, *Reticulitermes speratus*. The exceptionally hard wood of a Nigerian plant, *Xylopia aethiopica*, also withstands attack from termites and other insects destructive to wooden structures; this has led to the isolation of ent-kauranes, (−) kaur-16-en-19-oic acid which has a strong termite antifeedant activity against workers of *R. speratus* Kolbe [158]. Several natural neoclerodane diterpenoids isolated from *Linaria saxatilis* and some semisynthetic derivatives were tested against several insect species with different feeding adaptations. The antifeedant tests showed that the oliphagous *L. decemlineata* was the most sensitive insect, followed by the aphid *Myzus persicae*. The polyphagous *S. littoralis* was not deterred by these diterpenoids; however, following oral administration, some of these compounds did have post-ingestive antifeedant effects on this insect. In general terms, the antifeedant effects of these compounds were species-dependent and more selective than their toxic/post-ingestive effects. The study of their structure–activity relationships showed that both the decalin moiety and the chain at C-9 determined their bioactivity. Furthermore, the presence of a 4,18-epoxy/diol moiety was an

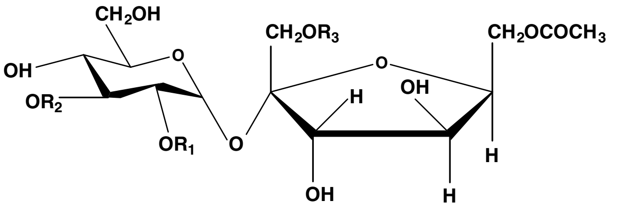


Figure 8 Sucrose ester

important feature for both the antifeedant and the toxic/post-ingestive effects [159]. On the whole, study of neo-clerodane diterpenoids from structural elucidation to biological activity has been extensively discussed recently [160] and many deterpenoids have been reported as both insecticidal and feeding deterrents against various insect species and discussed comprehensively [9, 13].

Sugar Esters

Plant glucose and sucrose esters occur naturally in glandular trichomes of leaves of wild tobacco *Nicotiana gossei*, *Lycopersicon typicum* and other solanaceous plants [161–164]. These esters are composed of lower fatty acids (C2 to C10) and have been found to be very effective against soft bodied insects.

Phytochemical investigations of *Nicotiana* sp. have resulted in the isolation of a variety of glucose esters [165, 166] and acyl sugars [167, 168] that deter insects. A series of sucrose esters (Figure 8) have been reported in the cuticular waxes of the tobacco leaves [169–171]. Three sucrose esters were isolated from the surface lipids of leaves of *Nicotiana cavicola* [172]. Common features found in all three sucrose esters were the presence of one acetyl residue at fructose ring and free hydroxyl groups at 2 and 3 positions of glucose ring. The presence of sucrose esters in wild tomato and wild potato species [173–175] has also been related to aphid resistance [168]. Glucose and sucrose esters reportedly disrupt the integrity of cellular membranes and uncouple oxidative phosphorylation, similar to the action of insecticidal soaps. According to Puterka and Severson [176], sugar esters disrupt the structure of the insect cuticle. It has been stated that leaf surface moisture and ambient relative humidity affected the efficacy of *N. gossei* sugar esters [177, 178]. For example, the application of the hygroscopic materials such as humectants at the site of application improve the toxicity of natural sugar esters from *N. gossei* and other *Nicotiana* species as well as certain synthetic sugars against tobacco aphids [177, 178].

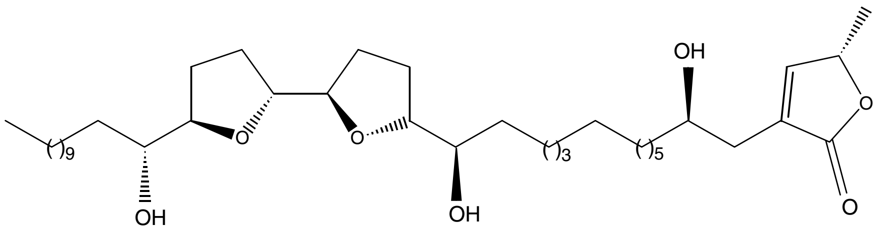
The product, first registered in 2002, contains 40% sucrose-based active ingredient. Functionally, this product appears to differ little from the insecticidal soaps based on fatty acid salts developed in the 1980s, particularly potassium oleate. Although useful in home and garden products and in greenhouse production, the utility of glucose and sucrose esters for agriculture remains to be seen, as no substantial activity has been recorded against lepidopterans (Koul *et al.*, unpublished data).

Acetogenins

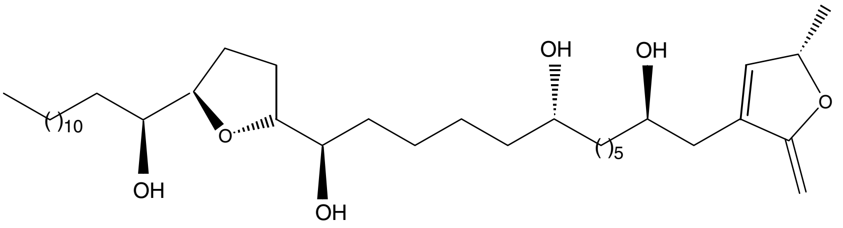
Bioactive acetogenins such as annonins (Figure 9), and related compounds namely squamocin, asimicin, annonacins and cohibinsin occur widely in twigs and branches, unripe fruits and seeds of several *Annona* (custard apple) species (Annonaceae). Entire group of annonaceous acetogenins has been patented as pesticide in which asimicin was claimed as a structurally defined pesticidal acetogenin. Johnson *et al.* [179] have isolated hundreds of acetogenins from the Annonaceae, and for many, their potential as anticancer agents exceeds their value as insecticides. According to Isman [17] Annona seed extracts may prove useful in tropical countries where the fruits are commonly consumed or used to produce fruit juice, in which case the seeds are a waste product. In fact, his group has demonstrated that crude ethanolic extracts or even aqueous extract of seeds from *Annona squamosa* collected at several sites in eastern Indonesia are effective against the diamondback moth, *P. xylostella*. Acetogenins are slow stomach poisons, particularly effective against chewing insects such as lepidopterans and the colarado potato beetle, *L. decemlineata*.

Light-activated Allelochemicals

Ultraviolet and sunlight usually play a counterproductive role in degradation of botanical pesticides, leading to decrease in their effectiveness. However, in some cases, toxicity of phytochemicals increases following their exposure to light radiation. Such light-activated phototoxins such as substituted acetylenes, thiophenes, acetylenic thiophenes, quinines, furanocoumarins and related compounds exhibit significant pest control properties. For example, oil of the desert plant *Artemisia monosperma* has been reported to contain a phototoxin 3-methyl-3-phenyl-1,4-pentadiyne that under light-induced conditions is as active as DDT against the housefly *M. domestica* and cotton leafworm *S. littoralis* larvae. Random screening of the plant *A. pontica* yielded an acetylenic epoxide, namely ponticaepoxide, which, when applied to the mosquito larvae under UV-light, exhibited an LC_{50} of 1.47 ppm. α-Terthienyl (αT), is found in abundance in the floral, foliar and root extracts of *Tagetes minuta*. It has been demonstrated that irradiation of αT with near UV-light, generates a reactive singlet oxygen species responsible for enhanced nematicidal activity. Under non-irradiated conditions it exhibited low toxicity to *Aedes* mosquito larvae and the activity was substantially increased upon irradiation by near UV light. An acetylenic thiophene



Asimicin



Annonacin

Figure 9 Structure of some active acetogenins

5-(3-buten-1ynyl)-2,2-bithienyl isolated from the *Tagetes* roots not only exhibited nematicidal activity but also showed insecticidal activity against several herbivorous insects such as *M. sexta* and *P. rapae*, and mosquitoes like *A. aegypti*. Under photosensitizing conditions, αT is more toxic (LC_{50}=20 ppb) to *A. aegypti* larvae than malathion (LC_{50}=62 ppb); and less toxic than chlorpyriphos (LC_{50}=1 ppb) and temephos (LC_{50}=3 ppb). The two polyacetylenic compounds, Metricaria ester and *cis*-dehydromatricaria ester, have been found to be ovicidal to freshly laid eggs of the fruitfly. Under the influence of UV light its activity was dramatically enhanced. Similarly, 2-(non-1-en-3,5,7-trinyl) furan exhibited excellent mosquitocidal activity against *A. aegypti* larvae exhibiting LC_{50} of 0.079 ppm under UV light. Photoactivated natural toxins generally operate by one of two modes of action. The phototoxin first absorbs light, and generates activated species of oxygen. In one mechanism of action, the excitation energy is then transferred to molecular oxygen to produce highly reactive singlet oxygen superoxide, hydroperoxide, or hydroxyl radicals through electron transfer mechanisms, which ultimately damage important biomolecules [180]. The other mode of action of phototoxins is photogenotoxic. These substances cause damage independently of oxygen by reacting directly with DNA [181, 182]. Since the mode of action of the phototoxins is quite different from the conventional synthetic pesticides, there is no likelihood of cross-resistance to conventional larvicides such as malathion [183]. However, light-induced toxicity to vertebrates and its possible effects on non-target organisms need further study before these are considered as an alternative to current mosquito larvicides. Finally, since phototoxins react with the light, they photodegrade quickly. Though this is an advantage with respect to toxic residues, it would require repeated applications to control insect populations.

Fungal Control

Numerous natural plant extracts and essential oils are germicidal and have potential for controlling of fungal diseases of crops. The extracts and essential oils from clove, cinnamon, origanum, mustard, cassia, radish, garlic, castor, canola and olive contain substances that are effective in inhibiting mycelial growth and/or spore germination of plant pathogens. Some hydrolytic compounds from these have been found to be fungicidal and can be formulated and used as alternatives for synthetic pesticides. The successful development of CH100, a product based on plant extracts, for controlling of wide range of plant diseases is a good example of such formulation and comprehensively discussed [184]. Many recent studies also supplement this view that botanical products could be useful to control agents of fungal pathogens. Methanol extracts from 27 medicinal plant species were tested at concentrations of 0.5, 1 and 2 mg/ml for their *in vivo* fungicidal activities against six phytopathogenic fungi. Their efficacy varied with plant pathogen, tissue sampled and plant species. Very strong fungicidal activity was produced by extracts of *Boswellia carterii*, *Saussurea lappa*, *Glycyrrhiza uralensis*, *P. nigrum*, *Rheum coreanum*, *Lysimachia foenum-graecum*, *Euodia officinalis*, *Santalum album* and *Curcuma longa* at 2 mg/ml. At 1 mg/ml, *S. album*, *P. nigrum* and *L. foenum-graecum* showed potent fungicidal activity against *Blumeria graminis* f. sp. *hordei*, *Puccinia recondita* and *Magnaporthe grisea*, respectively. *L. foenum-graecum* exhibited strong fungicidal activity against *M. grisea* at 0.5 mg/ml [185]. *Botrytis cinerea* is a most important pest of tomato in greenhouses and plant extract from the giant knotweed, *Reynoutria sachalinensis* has shown a high efficacy to control this powdery mildew [186]. Certain plant extracts from *Moringa oleifera*, *Vernonia amygdalina* and *Annona muricata* showed significant inhibitory growth effect against seed-borne infection of *Colletotrichum destructivum* on cowpea (*Vigna unguiculata*), comparable to benomyl treatment in the control of the pathogen [187]. In Africa, a number of such studies also show the efficacy of plant extracts against fungal pathogens, particularly yam rot [188], *Fusarium* [189] and *Penicillium*[190]. In Mexico, about 54 plant extracts from 20 different plant species have been recorded to control various fungi such as *Alternaria*, *Colletotrichum*, *Fusarium* and *Rhizopus* [191]. In India, many studies are available to show the efficacy of plant extracts against fungal pathogens [192, 193]. Aqueous extract of eight plants were screened for antifungal activity against *Fusarium solani* and *Aspergillus flavus*. The antifungal activity of aqueous extract of *Decalepis hamiltonii*, an edible plant, was further evaluated at different concentrations by the poisoned food technique against eight species of *Fusarium*, ten species of *Aspergillus*, three species of *Penicillium*, two species of *Drechslera* and *Alternaria alternata*. These phytopathogenic fungi were isolated from sorghum, maize and paddy seeds. It was observed that aqueous extract showed significant antifungal activity against all the test pathogens [194]. Olive leaf extracts are antifungal against 30 strains of various fungal species causing food-borne diseases and food spoilage [195]. As olive leaves are now shown to inhibit or delay the rate growth of range of fungi, they might be useful as natural preservatives.

Antifungal activities of certain essential oils or their components have also been assessed and found to be effective against *B. cinerea* [196], *Monilinia fructicola* [197], *Rhizoctonia solani*, *Fusarium moniliforme* and *Sclerotinia sclerotiorum* [198], *Fusarium oxysporum* [199], *Aspergillus niger* [200, 201], *A. flavus* [202], *Penicillium digitatum* [203] and *F. solani, R. solani, Pythium ultimum* and *Colletotrichum lindemuthianum* [204], *Alternaria padwickii*, *Bipolaris oryzae* and peanut fungi [22, 205]. Unlike insects, different fungal species show more consistent results. Greenhouse experiments have been conducted to determine the effectiveness of plant essential oils as soil fumigants to manage bacterial wilt (caused by *Ralstonia solanacearum*) in tomato. Potting mixture (‘soil’) infested with *R. solanacearum* was treated with the essential oils at 400 and 700 mg per litre of soil in greenhouse experiments. *R. solanacearum* population densities were determined just before and 7 days after treatment. Populations declined to undetectable levels in thymol, palmarosa oil and lemongrass oil treatments at both concentrations, whereas tea tree oil had no effect. Tomato seedlings transplanted in soil treated with 700 mg/l of thymol, 700 ml/l of palmarosa oil, and 700 ml/l of lemongrass oil were free from bacterial wilt and 100% of plants in thymol treatments were free of *R. solanacearum* [206]. Recently, strawberry fruit volatiles have been recorded to inhibit mycelial growth of *Colletotrichum acutatum* significantly [207].

The effect of essential oils, ethanolic and aqueous extract of 41 vegetable species on *Aspergillus* has been demonstrated using an *in vitro* screen. A total of 96 plant extracts were screened. Essential oils were found to be the most effective in controlling aflatoxigenic strains. Studies on percentage of germination, germ-tube elongation rate, growth rate and aflatoxin B_1 accumulation were the parameters inhibited by the plant products. Mountain thyme, clove essential oil and poleo treatments suggested that these products could be used alone or in conjunction with other substances to control the presence of aflatoxigenic fungi in stored maize [208].

Antifungal Compounds

Some allelochemicals have been reported to possess biological activity against fungal pathogens. Three different sesquiterpene lacones, viz. hydroxyachilin from *Artemisia lanata*, parthenolide from *Magnolia grandiflora* and dehydrocostuslactone and costunolide from costus resin oil have been reported to possess fungicidal activity [209].

Chemical investigation of the diethyl ether extract of the stem bark of *Khaya ivorensis* (Meliaceae) afforded ten limonoids of angolensates, ring D-opened limonoids and mexicanolides. These compounds were evaluated for their antifungal activity against the plant pathogenic fungus *B. cinerea*. Methyl 6-hydroxyangolensate and 3,7-dideacetylkhivorin were also tested for their antifungal and antibacterial activities on several fungal and bacterial species. Methyl angolensate and 1,3,7-trideacetylkhivorin displayed the highest antifungal activity against *B. cinerea*, with, respectively, 62.8 and 64.0% mycelial growth inhibition at 1000 mg/l, and 73.3 and 68.6% mycelial growth inhibition at 1500 mg/l. 3,7-Dideacetylkhivorin showed stronger antifungal and antibacterial activities than methyl 6-hydroxyangolensate against all of the test fungi and bacteria except *Penicillium expansum*. This is the first report on the antifungal and antibacterial effects of these limonoids [210].

Antifungal activities of natural substances from *Eucalyptus dalrympleana, E. globulus, Eucalyptus gunnii* and *Eucalyptus urnigera* were evaluated against post-harvest pathogens of kiwifruits, *B. cinerea*, *Botryosphaeria dothidea* and *Diaporthe actinidiae*, to screen effective natural substances as an alternative to chemical fungicides. Gallic acid was found to be effective in mycelial growth and spore germination of *B. cinerea* at relatively high concentrations. The results suggest that gallic acid can be a safer and more acceptable alternative to current synthetic fungicides for controlling soft rot decay of kiwifruit during post-harvest storage [211].

Thymol and carvacrol are definitely active against most fungal species tested [197, 198, 212]. The mechanism of action of these compounds against fungi is unknown but may be related to their general ability to dissolve or otherwise disrupt the integrity of cell walls and membranes [213].

Some allelochemicals have been shown to have substantial commercial potential, such as cinnamaldehyde against *Verticillium fungicola*, *Rhizoctonia*, *Pythium*, *Sclerotinia homoeocarpa* and *F. moniliforme*; a combination of L-glutamic acid and γ-aminobutyric acid against powdery mildew; a polysaccharide, laminarine, against *Septoria* and powdery mildews and milsana extract from giant knotweed, *R. sachalinensis* against *Botrytis* spp. [19] suggesting the potential of plant products in fungal pathogen control.

Herbicides

Weeds pose a recurrent and ubiquitous threat to agricultural productivity. Among the pests, weeds alone are held responsible for nearly 34% reduction in crop yield [214]. According to an Agrow [215] report, the total value of world's agrochemical market was between US$31–35 billion and among the products herbicides accounted for 48%, followed by insecticides (25%) and fungicides (22%). However, the excessive use of synthetic pesticides to get rid of noxious pests has resulted in several environmental hazards and to combat this efforts are being made world over to replace these synthetic chemicals with alternatives that are safer and do not cause any toxicological effects on the environment. The phenomenon of allelopathy, which is expressed through the release of chemicals by a plant, has been suggested to be one of the possible alternatives for achieving sustainable weed management. The use of allelopathy for controlling weeds could be either through directly utilizing natural allelopathic interactions, particularly of crop plants, or by using allelochemicals as natural herbicides [216, 217]. Synthetic herbicides continue to be a key component in most weed management strategies; however, in the recent past some progressive studies have been made in using plant-based products as weed control agents. Some studies have focused towards natural herbicides from plants [218–220]. During the last decade, emphasis has been on the use of plant extracts to control germination and growth of weed species; such as aqueous extracts of *Cirsium arvense* and *A. conyzoides* [221], *Ailanthus altissima* bark extract [222] and aqueous leaf extracts of some trees [223] to control weeds of wheat. Even rice by-products have been used for weed control [224]. Recently, methanolic extracts of 39 aquatic plants were screened for herbicidal activity. All extracts at 1% concentration suppressed the germination and seedling growth of *Echinocloa crus-galli* with remarkable effectivity. Seven plant species reduced the germination rate of *E. crus-galli* by >80%. The highest inhibitory activity on germination and germination rate was 62 and 87%, respectively [225].

Some studies also demonstrate the efficacy of plant products as weedicides in field situations. Extracts of *A. altissima* stem bark were evaluated for herbicidal effects under field conditions in two outdoor trials. The first field trial investigated the level of activity and selectivity of the extract. *A. altissima* bark extract was sprayed post-emergence onto 17 species of weeds and crops. Strong herbicidal effects were observed within several days. Even the lowest rate caused mortality and injury in excess of 50% for nine of the 17 species, and a significant reduction in shoot biomass for 13 species. The second field trial tested the ability of bark extract to control weeds under field conditions with horticultural crops (bush bean, cauliflower, sweetcorn and tomato). Extract treatment provided partial weed control (the greatest reduction in weed biomass was 40%), but also caused serious crop injury. Bush bean was the only crop that showed a significant increase in shoot biomass and fruit yield, compared with the non-weeded control. The herbicidal effects of *A. altissima* bark extract declined within the first few weeks after application, suggesting rapid degradation under field conditions [222]. Similarly, *Houttuynia cordata* Thunb is a medicinal plant that has now been shown to possess weed control properties in transplanted rice. Aqueous extracts from the dried powders inhibit the germination and initial seedling growth of two major weed species, viz., *Echinochloa* and *Monochoria* in rice paddy fields of Japan. Obviously, these results suggest that the dwarf lilyturf plants might be used as a natural herbicide to control weeds in rice field [226]. *T. minuta* leaf powder (1–4 t/ha) has also been used against two invasive weeds, *E. crus-galli* and *C. rotundus* in rice fields [227], which reduced the emergence of both weed species in field conditions.

Essential oils have also shown potential as herbicides. Dudai *et al.* [228] found that soil application of an essential oil from *C. citratus* (lemongrass) inhibited germination of both mono- and dicotyledonous plant species. The citronella oil is reported to have preemergence herbicide activity [229]. Some herbicidal compositions containing plant essential oils and mixtures or blends there of have been patented for controlling weeds and grasses [230]. Recently, use of eucalyptus oil against weeds has been established [231] and the oil is suggested to be an environmentally benign pest control product that is active against bacteria, fungi, insects and nematodes as well. Thus, ability of these natural plant products to kill or reduce weed/pest populations represents an alternative to the use of toxic weedicides.

Herbicidal Compounds

Allelochemicals are an important potential source for new herbicides [232–234] and agrochemicals since they offer new modes of action, more specific interactions with weeds, and potentially less environmental damage. However, despite extensive research, few natural products have been found with worthwhile herbicidal activity [235]. Some allelochemicals from plants have been used as leads for the discovery of synthetic herbicides with benign environmental properties, e.g. mesotrione [236, 237],

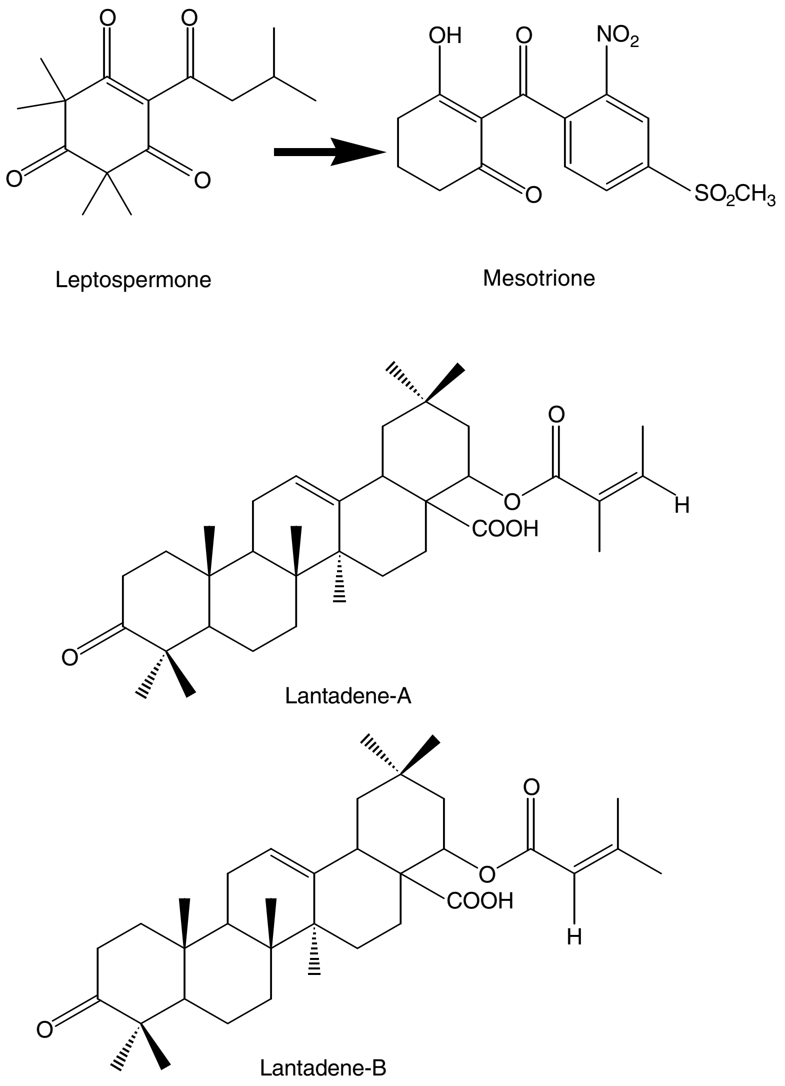


Figure 10 Examples of some herbicidal compounds. Mesotrione is derived from leptospermone from *Callistemon citrinus*

basically derived from a natural compound leptospermone (Figure 10) from roots of the bottle brush plant *Callistemon citrinus*.

Although natural product-based discovery strategies have not been as successful for herbicides as for other pesticides or pharmaceuticals, there have been some notable successes. Phosphinothricin, the biosynthetic version of glufosinate, and bialaphos are phytotoxic microbial products that have yielded commercial herbicides. Cinmethylin, a herbicidal analogue of cineole, has been sold in Europe and Asia. The triketone herbicides are derivatives of the plant-produced phytotoxin leptospermone [238]. Sesquiterpene lactones constitute a wide group of compounds with several biological activities, including allelopathic. The naturally occurring sesquiterpene lactones dehydrocostuslactone and cynaropicrin and their modified forms have been reported as active herbicides against *Lactuca sativa*, *Lolium rigidum* and *E. crus-galli*. This study suggests that guaianolides may be good candidates for the development of new natural-product-based herbicides [239]. *A. altissima* bark, extracted with methanol has been shown to yield ailanthone as one of the major herbicidal compounds [240]. Further, the allelochemicals of some weedy species can be extracted, purified and used directly like synthetic herbicides. Parthenin from ragweed parthenium (*Parthenium hysterophorus*) [241, 242] and artemisinin from *Artemisia* sp. are well-known examples [236, 243, 244]. Recently, Fujii and Hiradate [245], in the search for natural chemicals useful as herbicides have demonstrated that cyanamide from *Vicia villosa*, *L-DOPA (3,4-dihydroxy-L-phenylalanine) from Mucuna pruriens* and *cis*-cinnamic acid from *Spiraea thunbergii* are herbicidal on the basis of biological activity per unit weight of the organism, suggesting the total activity as a function of the specific activity of natural chemical and their content in the plant. For this purpose, the 'Weed Suppression Equation' has been devised [245]. This is an interesting concept because in the field, it is important to discriminate and evaluate the contribution of allelopathy with competition for abiotic and biotic factors and use of the equation concept suggests the potential to discriminate between these factors.

Eugenol, a known essential oil compound, has some herbicidal properties and its derivatives do inhibit weed growth significantly [246]. Citronella allelochemicals at a high dose largely killed foliage of some tree species within 1 day of application but most species regrew strongly. *Senecio jacobaea* was the most susceptible species, with good control two months after application of the higher dose [229] and volatile cineoles are also allelopathic to weedy plant species [247]. Juglone from walnut trees is effective against redroot pigweed, velvet leaf and barnyard grass. Dhurrin from sorghum, gallic acid from spurge, trimethylxanthene from coffee and cinch from eucalyptus are some other important plant products with potential herbicide activity [248]. However, these products represent only a small fraction of commercialized herbicides, but they have each introduced a novel molecular target site for herbicides.

A recent comprehensive review on allelopathic interactions and allelochemicals for possible sustainable weed management describes the role of number of allelochemicals in weed management, suggesting that allelochemicals present in the higher plants can be directly used for weed management on the pattern of herbicides and their bioefficacy can be enhanced by structural changes or the synthesis of chemical analogues based on them. It is also proposed that the production of allelochemicals can be enhanced or the transgenics with foreign genes encoding for a particular weed-suppressing allelochemical could be produced using both conventional breeding and molecular genetic techniques [217]. However, with conventional breeding being slow and difficult, more emphasis is laid on the use of modern techniques such as molecular markers and the selection aided by them with a hope that promising results could be expected in future [217].

In some recent studies, some potential allelochemicals have been studied with herbicidal potential. Aqueous extract of kava roots showed high allelopathic potential and strongly suppressed germination and growth of lettuce, radish, barnyardgrass and monochoria. Nine kava lactones were detected using Gas chromatography-mass spectromentry (GC-MS) including desmethoxyyagonin, kavain, 7,8-dihydrokavain, hydroxykavain, yagonin, 5,6,7,8-tetrahydroxyyagonin, methysticin, dihydromethysticin and 11-hydroxy-12-methoxydihydrokavain. There were notable quantities of desmethoxyyagonin, kavain, 7,8 dihydrokavain, yagonin, methysticin and dihydromethysticin, and these six major lactones in kava roots showed great herbicidal and antifungal activities. Growth of lettuce and barnyardgrass were significantly inhibited at 1–10 ppm, and *Colletotrichum gloeosporides*, *F. solani*, *F. oxysporum* and *Trichoderma viride* were significantly inhibited at 10–50 ppm. The biological activities of kava lactones were characterized by different double-bond linkage patterns in positions 5,6 and 7,8. This study suggests that kava lactones may be useful for the development of bioactive herbicides and fungicides [249]. Similarly, allelochemicals from *Lantana camara* against aquatic weeds *Eichhornia crassipes* and *Microcystis aeruginosa* have been shown to inhibit their growth and the compounds responsible belong to pentacyclic terpenoids, lantadene A and B (Figure 10) [250] suggesting that these allelochemicals could potentially be used to improve the management of weeds in aquatic systems.

Extracts versus Allelochemicals: Comparative Impact

Plants are not only able to synthesize individual defence metabolites with diverse chemical structures but also produce complex mixtures of defence compounds, such as the limonoids in rutales or terpenes of essential oils. Many of the individual constituents are acutely toxic to insects and pathogens, as discussed above. However, the toxicity of these compounds can be potentiated in mixtures, so that the activity of the mixture is higher than would be expected by adding up the activities of its individual constituents. This phenomenon, known as synergism, has recently been demonstrated for mixtures of limonoids [112, 113, 251] or essential oil constituents [252–254]. These mixtures were more toxic than would have been expected from the simple additive effects of the constituents. The mechanisms behind such synergisms are unknown, but may involve the ability of one component of a mixture to inhibit the detoxification of others or to enhance the absorption of others from the gut. One can surmise that synergism may be the result of phytochemicals inhibiting an insect's ability to employ detoxifying enzymes against synthetic chemicals. Mixtures of plant extracts with compounds showing synergistic or potentiating interactions between them are considered to have a higher and longer-lasting effect [255]. Identifying these synergist compounds within mixtures may lead to the development of more effective pesticides as well as the use of smaller amounts in the mixture to achieve satisfactory levels of efficacy. Scott *et al.* [256] demonstrated that the amides present in the *Piper* plants have higher toxicity when they are combined in binary, tertiary and quaternary mixtures as is also suggested by the fact that seed extracts of piper plants may be more powerful than the isolated compounds [82]. There are no simple explanations for the observed differences in the efficacy of the whole extract from different parts of the plant and the isolated compounds; however, variations in the concentrations of the insecticide compounds among the plant tissues suggest that varied selective pressures operate in the plants, and a great number of combinations of compositions can arise inside individuals in certain species [257], which can provide a higher protection level to the plant against herbivores [258]. Obviously, this implies that plant extracts afford more impact in terms of pest control than the individual allelochemicals. Mixtures of defence compounds may be a deterrent to pests for longer periods than single compounds as a result of effects at the sensory level [259]. Mixtures of terpene-containing compounds with different physical properties may allow more rapid deployment or longer persistence of defence. An example of such a mechanism seems to occur in conifer resin, which is a mixture of (i) monoterpene olefins (C10) with antiherbivore and antipathogen activity and (ii) diterpene acids (C20) that are toxic and deterrent to herbivores [260].

Another impact that a combination of compounds in a plant extract could make is variable response of enzymes towards different compounds suggesting more potential in the control of a pest. For instance, antifeedant activity of a mixture of limonoids 1,7-di-*O*-acetylhavanensin and 3,7-di-*O*-acetylhavanensin isolated from seeds of *Trichilia havanensis* (Meliaceae), and the *neo*-clerodane diterpene scutecyprol A, isolated from *Scutellaria valdiviana* (Lamiaceae), on fifth instar larvae of the beet armyworm, *Spodoptera exigua* has been determined. Choice and no-choice feeding assays, nutritional tests and post-treatment studies indicated that scutecyprol A acts as an insect feeding deterrent against *S. exigua*, whereas the antifeedant activity of mixture is likely associated with a toxic mode of action. The mixture of limonoids significantly increased glutathione *S*-transferases during the treatment and post-treatment periods, whereas esterases were inhibited during the treatment period. On the contrary, scutecyprol A did not have any significant effect on any of the enzymatic processes. Hence, the metabolic response of *S. exigua* larvae to the ingestion of the secondary metabolites tested depends on their mode of action [261], suggesting a mixture of limonoids may be a useful control agent and thereby play a relevant role in pest management, particularly when insecticide resistance has developed as a result of elevated esterase activity.

From the resistance point of view, the short residual life of plant insecticides may be considered as a positive, since there will be a very low probability that two extracts would always be identical so that selective pressure on the pest species will not always be the same. Even if all the same compounds are found in the extract, concentrations almost always will be different. Generally, insect resistance takes longer time to develop to a mixture of natural active compounds than to any one individual component. This may be because it is more difficult to detoxify a compound complex than a single molecule.

Commercial Impact

Many extracts and individual allelochemicals from plant sources so far have given excellent results in laboratory conditions. In field situations, only a few of them are satisfactory alternatives to traditional pest management. Chemical control usually involves broad-spectrum insecticides, and they have to be broad-spectrum by necessity. They have to sell in large enough amounts to accommodate financial development, research and marketing. The class of plant products is tested against one or a small group of insects attacking a specific crop. As a compound, it inhibits the feeding of one species, but for another it may be ineffective or just an attractant or growth inhibitor. Thus, replacement of a traditional chemical with a specific allelochemical will make pest management more expensive [4].

Among the traditional botanicals, in the USA the botanicals registered for use are pyrethrum, neem, rotenone, sabadilla, ryania and nicotine. Several azadirachtin-based insecticides are sold in the USA and a number of essential oils are exempt from registration. Canada has been more conservative where only pyrethrum, rotenone, nicotine are registered for use. Mexico, of course allows the products registered in the USA. In Europe, pyrethrum, neem and nicotine are allowed, however, since 2008 rotenone is no longer allowed in the European Union. In fact, neem has still to make headway in these countries. In Asia, India leads in the use of botanicals where a number of products are registered under provisional registration. According to Isman [17], neem-based products are in abundance in addition to pyrethrum, rotenone, nicotine and essential oils. However, neem is yet to be approved in Australia, New Zealand and the Philippines. In Latin America, Brazil leads in the registered products based on pyrethrum, rotenone, neem, garlic and nicotine. Throughout Latin America, plant oils and extracts are produced by cottage industry. However, data on regulated products for most African countries is not known. Apparently, only pyrethrum is approved for use in South Africa.

Among the latest commercial botanicals, the only prospect seems to be the neem-based products. However, apart from neem products, there are a few actual demonstrations of antifeedant efficacy in the field. Application of polygodial or methyl salicylate at the IARC Rothamsted have shown that aphid populations are reduced with concomitant increases in yields of winter wheat, in one case comparable to that achieved with the pyrethroid insecticide cypermethrin [262]. Similarly, toosendanin, an antifeedant limonoid from the bark of the trees *Melia toosendan* and *M. azedarach* (Meliaceae) has been subjected to considerable research as a botanical pesticide [36, 90, 263]. Vertebrate selectivity of this compound is very favourable (LD_{50} mice=10 g/kg) [264]. Production of a botanical insecticide based on toosendanin, using a refined bark extract containing approximately 3% toosendanin (racemic mixture) as the active ingredient, has recently begun in China. Toosendanin-based insecticides could become a potential commercial product worldwide as formulations based on the technical concentrate are under evaluation in Canada to assess its potential against pests of agriculture and forestry in North America.

BioProspect Limited is a Brisbane-based biotechnology company that is currently focused on the development of two products; natural termite compound Termilone® (based on false sandalwood, *Eremophila mitchelli* oil) and the Bioeffectives® range of natural plant extracts for application in agricultural markets (http://www.bioprospect.com). This company hopes to make a substantial impact in an environmentally friendly solution to the billion-dollar termite damage problem as current treatments are increasingly coming under the microscope for their hazardous nature.

Among plant essential oils, surprisingly few pest control products have appeared in the market place. This may be a consequence of regulatory barriers to commercialization (i.e. cost of toxicological and environmental evaluations) or the fact that efficacy of essential oils toward pests and diseases is not as apparent or obvious as that seen with currently available products. In the USA, commercial development of insecticides based on plant essential oils has been greatly facilitated by exemption from registration for certain oils commonly used in processed foods and beverages [265]. This opportunity has spurred the development of essential oil-based insecticides, fungicides, and herbicides for agricultural and industrial applications and for the consumer market, using rosemary oil, clove oil and thyme oil as active ingredients. Interest in these products has been considerable, particularly for control of greenhouse pests and diseases and for control of domestic and veterinary pests, and some US companies have introduced essential-oil-based pesticides in recent years. Mycotech Corporation produced an aphidicide/miticide/fungicide for greenhouse and horticultural use and for bush and tree fruits based on cinnamon oil with cinnamaldehyde (30% in the EC formulation) as the active ingredient; however, this product is no longer being sold. EcoSMART Technologies has introduced insecticides containing eugenol and 2-phenethyl propionate aimed at controlling crawling and flying insects, under the brand name EcoPCO® for pest control professionals. An insecticide/miticide containing rosemary oil as the active ingredient has recently been introduced for use on horticultural crops under the name EcoTrol™. Another product based on rosemary oil is a fungicide sold under the name Sporan™, while a formulation of clove oil (major constituent: eugenol), sold as Matran™, is used for weed control. All of these products have been approved for use in organic food production. The primary active ingredients in EcoSMART products are exempt from US Environmental Protection Agency registration and are approved as direct food additives or classified as GRAS (generally recognized as safe) by the US Food and Drug Administration. Recently, EcoSMART has developed Hexa-Hydroxyl®, a synergistic blend of plant oils effective against a broad spectrum of pests. It is claimed to work in the same way as natural pyrethrins. The product is safe as per FDA regulations (http://www.pestweb.com).

Several smaller companies in the USA and the UK have developed garlic-oil-based pest control products and in the USA there are consumer insecticides for home and garden use containing mint oil as the active ingredient. Menthol has been approved for use in North America for control of tracheal mites in beehives, and a product produced in Italy (Apilife VAR™) containing thymol and smaller amounts of cineole, menthol and camphor is used to control Varroa mites in honeybees (Canadian Honey Council; http://www.saskatchewanbeekeepers.ca/users/folder.asp@FolderID=5317.htm).

The humble marigold could be the key to organic, renewable and cost-effective pest control, according to researchers at De Montfort University (DMU) in Leicester, UK. *Tagetes patula*, the French marigold species most common to gardens, has the ability to destroy attackers beneath the soil and it is this property that researchers believe could be harnessed to help protect crops.

Israel start-up Botanocap, founded on oil encapsulation knowledge created at the Ben Gurion University of the Negev, is developing a slow-release technology for essential oils, to make relatively environmentally friendly pesticides. The company has developed a patented technology for the gradual release of essential etheric oils and natural components. It possesses patents on capturing essential oils in capsules, to achieve the delayed release effect. Etheric oils can be produced from some 3000 plants. Controlled slow release with protection of the active components until release are the main points of Botanocap (http://www.ivc-online/ivcWeeklyItem.asp?articleID=5313).

Marrone Organic Innovations, Inc. in the USA has introduced Regalia® SC, for controlling both fungal and bacterial diseases in a wide range of fruit, vegetable and ornamental crops (http://www.marroneorganicinnovations.com). Regalia® SC, an EPA registered product, is an extract from giant knotweed, *R. sachalinensis* and more than 100 field trials have demonstrated the product's performance. The extract of the pink plume poppy (*Macleaya cordata*) has been registered for use as fungicide under the trade name Qwel by Camas. The extract is a mixture of several alkaloids. The target pathogens are powdery mildew, *Alternaria* leaf spot and *Septoria* leaf spot in ornamental crops. It is sold as a 1.5% aqueous extract (http://epa.gov/pesticide/biopesticide/ingredients).

In case of natural herbicides, at present, two bioherbicides are being marketed for the control of specific weeds that are normally hard to control: DeVine for control of strangler vine in Florida citrus and Collego for control of northern jointvetch in rice and soybeans in Arkansas, Louisiana and Mississippi. DeVine has been so successful in destroying strangler vine that the market for the product has almost been lost. The reason for its great effectiveness is that the product remains in the soil and gives 95–100% control for 6–10 years after a single application (http://www.ces.ncsu.edu).

Constraints

From crop protection point of view, plant-based products should meet the same criteria as insecticides. That means they should be selective to the target pests and must have sufficient residual action to protect the crop through its window of vulnerability to the key pests [266]. There is also significant variability and interspecific differences in bioactivity. For instance, azadirachtin, the potential botanical allelochemical, has been evaluated against more than 500 pest species [87] showing about 40-fold variability in its activity. An investigation with silphinene sesquiterpenes as antifeedants has revealed profound differences in activity when tested against cotton leafworm, the Colorado potato beetle and five species of aphids [267].

In terms of specific constraints, the efficacy of these materials falls short when compared with synthetic pesticides although there are specific pest contexts where control equivalent to that with conventional products has been observed. Essential oils also require somewhat greater application rates (as high as 1% active ingredient) and may require frequent reapplication when used out-of-doors.

Additional challenges to the commercial application of plant-based pesticides include availability of sufficient quantities of plant material, standardization and refinement of pesticide products, protection of technology (patents) and regulatory approval [268]. In addition, as the chemical profile of plant species can vary naturally depending on geographic, genetic, climatic, annual or seasonal factors, pesticide manufacturers must take additional steps to ensure that their products will perform consistently. All of this requires substantial cost and smaller companies may not be willing to invest the required funds unless there is a high probability of recovering the costs through some form of market exclusivity (e.g. patent protection). Finally, once all of these issues are addressed, regulatory approval is required. Although several plant essential oils are exempt from registration in the USA, many more oils are not, and few countries currently have such exemption lists. Accordingly, regulatory approval continues to be a barrier to commercialization and will likely continue to be a barrier until regulatory systems are adjusted to better accommodate these products [213].

Among botanicals, feeding deterrents make the major category of extracts or allelochemicals that have been evaluated against variety of pests [9], therefore, if used indiscriminately, may also result in development of resistance. This has been indicated in the studies of selection of resistance to azadirachtin in the green peach aphid, *M. persicae* [269]. Another operational problem is the potential for rapid desensitization to a feeding deterrent. Individual insects initially deterred by a feeding inhibitor, become increasingly tolerant upon repeated or continuous exposure. This has been demonstrated in the case of azadirachtin and toosandanin used against tobacco cutworms [270]. In fact, insects becoming habituated and cross-habituated is a serious limitation of feeding deterrents; however, it can be mitigated by using mixtures of antifeedants in a multicomponent strategy as previously suggested for the non-azadirachtin type of compounds [112, 113] and demonstrated in the combination of xanthotoxin and thymol [266].

Overall, there appear to be three basic barriers to commercialization for botanical biopesticides, i.e. sustainability of the botanical resource, standardization of complex extracts and regulatory approval. Another aspect that is a matter of concern is the processes of intellectual property rights (IPR), because plant-based products are directly related to regional biodiversity. IPR issues are being debated among academics, policy-makers and non-governmental organizations. The main questions asked are ‘Who does what kind of research or development?’ and ‘How can smallholder farmers benefit, with increasing number of players and opportunities, as well as changing roles of different actors and institutions?’ IPR rules extend globally and have wide-ranging implications on the use of agriculture biodiversity, and conventions are still being worked out around the world. Imposition of intellectual property (IP) will have implications on the strategies developed by workers as there is a direct impact on protection of indigenous knowledge. The use of IP will require introduction of new organizational cultures among researchers who will have to use IP to protect their products which are of public goods by nature, to protect their access to scientific methods and applications, and to protect the end products, although IP does hold the prospect to commercialize research products as a means of funding future research and rewarding innovative researchers. This will require new skills and expertise to assist in proper understanding and application of IP issues more so for patenting of known indigenous knowledge. For instance, the rules of the *General Agreement on Tariffs and Trade/World Trade Organization* (GATT/WTO) on intellectual property have serious concerns in Indian economic circles. Patents are always national in character. Nevertheless, under the rules of the GATT/WTO, India has to eliminate the exclusions in its patent law. An additional question concerns the control over biological resources (e.g., neem is originally native to southeast and southern Asia). Issues such as how and who compensates developing countries or farmers for the use of ‘their’ biological resources remains an important issue even today.

Future Outlook

The practice of using products from plant sources allows us to develop and exploit naturally occurring plant defence mechanisms, thereby reducing the use of conventional pesticides. However, most of these new strategies need to be developed with four basic facts in mind: organize the natural sources, develop quality control, adopt standardization strategies and modify regulatory constraints. In fact, all the four areas need substantial effort, if plant-based products are to be successful and competitive. This will definitely give rise to a number of challenges and unexpected problems. For instance, limonene is known to be a bitter antifeedant, but at higher concentrations does cause irritation and allergic reactions when in contact with skin. Therefore, deeper cooperation between industrial and academic research is required that could definitely accelerate the process and give us new environmentally safe methods in future plant protection via plant defence mechanism of secondary metabolites. Creative strategies need to be deployed. For example, two methods of combining the use of teflubenzuron with insect antifeedant have been studied [271]. The strategy of applying the antifeedant and growth inhibitor together relies on stopping the overshoot in feeding that occurs when the insects are poisoned by teflubenzuron. The insect needs to eat $<1\%$ of the leaf disc to acquire a toxic dose but, in the absence of an antifeedant, it eats $>40\%$ even at the highest doses, during the lag phase that occurs between treatment and effect. In laboratory conditions, the combination of antifeedant with teflubenzuron decreased feeding damage by *P. xylostella* and *P. cochleariae* without diminishing the toxic effect [271]. In the alternative strategy, teflubenzuron and antifeedant were applied separately. Treatment of the growing tips of mustard plants with antifeedant forced insects down the plant to the lower leaves, where they were killed by diflubenzuron. Combination of an antifeedant with a physiological toxin (both may be from the plant source itself) is another choice to develop a sustainable pest management strategy based on plant products. Manipulation of insect population in this way now forms part of various insect control studies, such as the stimulo-deterrent diversionary cropping [272] and the push–pull strategies [273–275]. There are thus the opportunities such as: (i) changing consumer preferences towards the use of 'natural' over synthetic products; (ii) the existence of and growth in niche markets, where quality is more important than price; (iii) strong growth in demand for essential oils and plant extracts; (iv) the potential to extend the range of available products including new product development through biotechnology and (v) the production of essential oils and plant extracts from low-cost developing countries [28].

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Allelochemicals with negative allelopathic effects are an important part of plant defense against herbivory.[1][2]. The production of allelochemicals are affected by biotic factors such as nutrients available, and abiotic factors such as temperature and pH. Allelopathy is characteristic of certain plants, algae, bacteria, coral, and fungi. Allelopathic interactions are an important factor in determining species distribution and abundance within plant communities, and are also thought to be important in the success of many invasive plants.Â In: Chemical Ecology of Plants: Allelopathy in aquatic and terrestrial ecosystems, Mallik, A.U. and anon., Eds. Birkhauser Verlag, Basel, Switzerland. Comparing impacts of plant extracts and pure allelochemicals and implications for pest control. CAB Rev., 4: 1-30. Leroy, P. D., Schillings, T., Farmakidis, J., Heuskin, S., Lognay, G., Verheggen, F.J., Brostaux, Y., Haubruge, E. and Francis, F., 2012.Â J. Ent., 97: 533-538. https://doi.org/10.14411/eje.2000.082. Morrison, W. P. and Peairs, G.B., 1998. Response model concept and economic impact. In: Response model for an introduced pest â€“ the Russian wheat aphid (eds S.S. Quisenberry and F.B. Peairs). Entomological Society of America, Lanham MD, pp. 1-11. Reed, H. C., Reed, F.K. and Elliot, N.C., 1992. Comparing impacts of plant extracts and pure allelochemicals and implications for pest control. CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources 4: 1-30. Koul O., Walia S., Dhaliwal G. S. 2008.Â Regnault-Roger C., Philogene B. J. R. 2008. Past and current prospects for the use of botanicals and plant allelochemicals in integrated pest management. Pharm. Biol.