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Biopesticides

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Piopesticides

Summary : *A pesticide is any compound or formulation used to control pests which contains active ingredients and other substances to aid its delivery to target organisms and hence minimize pests. The major types of pesticides are herbicides, fungicides, rodenticides, molluscicides, soil bacteriostants, disinfectants, and living organisms with pesticidal activity. Pesticides are widely used in agriculture and have a tremendous impact on the production of food and fibres. They are important to the economy in terms of agricultural production, structure preservation and control of disease vectors. Biopesticides are often effective in very small quantities and decompose quickly, thereby resulting in lower exposures and largely avoiding the pollution problems caused by conventional pesticides.In addition to general information about pesticides; properties, chemistry and classification of biopesticides are also given in this review.*
Keywords : *Biopesticide, pesticide, pest.*

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Biopestisitler

Özet : *Pestisit, hedef organizmalara dağılımı sağlayan ve böylece pestleri azaltan aktif bileşenler ve diğer maddeleri içeren, pestleri kontrol etmek için kullanılan bir bileşik ve formülasyondur. Pestisitlerin ana tipleri; herbisitler,fungusitler, rodentisitler, molluskisitler, toprak bakteriyostantları, dezenfektanlar ve pestisit aktiviteye sahip canlı organizmalardır. Pestisitler, ziraatte yaygın şekilde kullanılır ve besin ile lif üretiminde büyük bir etkiye sahiptir. Bunlar hastalık etkeni vektörlerin kontrolü, yapı koruması ve ziraii üretim bakımından ekonomide önemlidir. Biyopestisitler çok küçük miktarlarda bile etkilidir ve geleneksel pestisitlerin sebep olduğu kirlilik problemlerinden geniş ölçüde kaçınma ve daha az maruziyetle sonuçlanmasına neden olarak hızlı bir şekilde dekompoze olurlar.*

Pestisitler hakkında genel bilgiye ilave olarak; bu derlemede, biyopestisitlerin özellikleri, kimyası ve sınıflandırılması da verilmektedir.
Anahtar kelimeler : *Biyopestisit, pestisit, pest.*

INTRODUCTION

A pesticide is any compound or formulation used to control pests which contains active ingredients and other substances to aid its delivery to target organisms and hence minimize pests. The major types of pesticides are herbicides, fungicides, rodenticides, molluscicides, soil bacteriostants, disinfectants, and living organisms with pesticidal activity.

In practice, mixtures of pesticides rather than single agents are often applied and this practice can lead to synergism or potentiation resulting from interaction between pesticides or among the ingredients of a formulation. Through the careful use of pesticides, humans have benefited by having an increased abundance of foods. It is estimated that 5 million tons of pesticides have been applied annually throughout the world, 70% of them being used for agriculture and the remainder by public health agencies.

The term pest derives from the Latin "pestis" for plague and is used to describe plants (weeds), vertebrates, insects, mites, pathogens and other organisms that occur where they are not wanted[1,2]. A

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pesticide is also intended for use as a plant regulator, defoliant, or desiccant[3].

Pesticide is a general classified term which includes the following groups[4]:

Algicides: Control algae in lakes, canals, swimming pools, water tanks.
Antifouling agents: Kill or repel organisms that attach to underwater surfaces.
Antimicrobials: Kill microorganisms such as bacteria and fungi.
Attractants: Attract pests.
Avicides: Kill birds.
Biocides: Kill microorganisms.
Disinfectants and sanitizers: Kill or inactivate disease-producing microorganisms on inanimate objects.
Defoliants: Cause leaves or other foliage to drop from a plant, usually to facilitate harvest.
Dessicants: Dry up animals and plants.
Fungicides: Kill fungi.
Fumigants: Produce gas or vapor intended to destroy pests in buildings or soil.
Herbicides: Kill weeds and other plants that grow where they are not wanted.
Insecticides: Kill insects and other arthropods.
Insect growth regulators: Disrupt the moulting, maturity from pupal stage to adult, or other life processes of insects.
Miticides: Kill mites that feed on plant and animals.
Microbial pesticides: Microorganisms that kill, inhibit, or out compete pets, including insects or other microorganisms.
Molluscicides: Kill snails and slugs.
Nematocides: Kill nematodes.
Ovicides: Kill eggs of insects and mites.
Pheromones: Biochemicals used to disrupt the mating behavior of insects.
Piscicides: Kill fish.
Plant growth regulators: Alter the expected growth, flowering, or reproduction rate of plants.
Repellents: Repel pests, including insects and birds.
Rodenticides: Control mice and other rodents.

Background

In the history, the use of natural pesticides has been known since the time of Homer. Chinese and Greeks used insecticidal substances 3,000 years ago. The earliest records on the insecticide use is sulfur, the burning of "brimstone" as a fumigant. However most of the ancient insecticides used were gall from a green lizard to protect apples from worms and rot, extracts of pepper and tobacco, soapy water, whitewash, vinegar, turpentine, fish oil, brine, lye, and many others[5-7].

Modern use of pesticides dates back from 1865 in the U.S.A. Use of synthetic pesticides became popular in the early 20th century. Development of DDT in 1939 and the discovery of its great insecticidal properties gave a tremendous impetus to use of insecticides. In 1939 there were 32 pesticide products registered in the U.S.; in 1993 there were 22.000[8]. When DDT and the new synthetic organic insecticides proliferated, they were thought to be the solution to all problems of feeding mankind and eliminating vectors of deadly diseases in humans and domestic animals. Firstly with the documentation of housefly resistance to DDT by 1947, the resistance soon developed in pests, particularly in insects treated with new pesticides[7]. The use of DDT was stopped in 1973 by the EPA (Environmental Protection Agency)[5]. The cyclodienes appeared after World War II. Although they were the most effective termiticides, agricultural uses of cyclodienes were cancelled by the EPA between 1975-1980. In addition to DDT, some other organochlorins (DDD, diicofol, ethylan, chlorobenzilate, and methoxyclor), organophosphates (malathion, trichlorfon, ethyl-parathion, and diazinon), organosulfurs (tetradifon, propargite, ovex), carbamates (carbaryl, methomyl, aldicarb, oxamyl, bendiocarb, and fenoxycarb), formamidines (amitraz, formetanate, and chlordimeform), dinitrophenols (binapacryl and dinocap), organotins (cyhexatin and fenbutatin-oxide), and acylureas (chlorfluazuron, teflubenzuron, flufenoxuron, and flucycloxuron) emerged on the market as the other synthetic insecticides. However, because of inherent toxicity, the dinitrophenols have all been withdrawn[5]. Pesticide resistance is the result of an increase in the ability of populations of a pest species to survive pesticide application[9].

Importance of pesticides

Natural biodata in the ecosystem reports 5-10 million species in the world. Most of these natural species are essential for the quality of the environment and survival of humankind. Despite their value for agriculture, pesticides have also possessed direct and indirect threats to the health of humans and to the environment around the world. There are approximately 1000 pesticide formulations in use throughout the world. It has been estimated that fewer than 0.1% of the pesticides applied to crops reaches the target pests; more than 99% of applied pesticides have the potential to impact non-target organisms (humans, fishes, and birds). Therefore, high priority should be given to developing pesticides with increased selectivity toward pest species and reduced damage to non-target organisms.

Human beings need to use pesticides during their lives. Because farmers have contended with some 80.000 plant diseases, 30.000 species of weeds, 1.000 species of nematodes, and more than 10.000 species of insects. Today, national and international agricultural organisations estimate that as much as 45 % of the worldís crops continue to be lost to these types of hazards[10].

Adverse effects of pesticides

Pesticides are toxic substances deliberately added to the environment. Pesticide residues contaminate birds, fish, wildlife, domestic animals, livestock, and human beings. There is abundant evidence of the risk which toxic pesticides pose particularly to human health. Most worrisome from a public health perspective are chronic health effects such as cancer, infertility, miscarriage, birth defects, and effects on the brain and nervous system[1,11]. An example of the adverse effects of synthetic pesticides is DEET, the active ingredient in many insect repellants. DEET is responsible for more than 5.000 poisonings every year in the U.S. (National Capitol Poison Center, Georgetown University Hospital, Washington, D.C.). DEET can cause central nervous system disturbances, dermatitis, and such irritation. According to 1995 data compiled by the American Association of Poison Control Centers, pesticides ranked seventh as the most common cause of poison exposure[11]. Children and individuals with impaired immune systems are more vulnerable than adults to pesticide poisonings[12].

Biopesticides

Pesticides are also originated from plant and microbial defense mechanisms. Biologically derived chemicals are important because of having less environmental toxicity. Development of azoxystrobin (β-methoxy acrylate) fungicides (produced by edible forest mushrooms) and spinosad (tetracyclic macrolides produced by *Saccharopolyspora spinosa*) pesticides are good examples of discovered biopesticides.

Chemical defences employed by terrestrial and marine organisms have proved to be valuable sources of novel chemotypes providing lead compounds for agrochemicals known as biopesticides.

There are several reasons for developing for alternative pesticides to the synthetic chemical pesticides for controlling pests. One of the important problems has been a significant level of resistance developing in current insecticides. Other reasons are their toxicological and environmental risks[13]. Biopesticides are often effective in very small quantities and decompose quickly, thereby resulting in lower exposures and largely avoiding the pollution problems caused by conventional pesticides.

Classification

Biopesticides have been classified into eight classes due to their chemical structures:
- Polyhalogenated monoterpenes
- Polyhalogenated C-15 metabolites
- Diterpenoids
- Peptides
- Amino acids
- Phosphate esters
- Sulfur-containing compounds
- Macrolides

Biopesticides have also been placed into three major categories due to their origins[14]:

Microbial pesticides

Microbial pesticides contain a microorganism such as a bacterium, fungus,virus or protozoan as the active ingredient. These pesticides can kill many different kinds of pests. The most widely used microbial pesticides are various types of the *bacterium Bacillus thuringiensis,* or with the common name "Bt", which can control specific insects in cabbage, potatoes, and other crops. Another type of Bt kills mosquitoes, but is ineffective against crop pests. Bt acts by producing a protein that kills the larvae of specific insects pests[14-17]. *B. t. kurstaki* and *B. t. aizawai* kill caterpillars. *B. t. israelensis,* one of the biological larvacides which is commercially available, kills larvae of Colorado potato beetle and elm leaf beetle. *Bacillus popilliae* or *B. lentimorbus* are also effective in controlling the larval stage (white grub) of Japanese beet[18,19].

Photorhabdus luminescens, a bacteria found recently, is considered to be an alternative to Bt. The toxins produced by *Photorhabdus* are active against a wide range of insects and are at least as potent as Bt[20,21]. In nature, *Photorhabdus bacteria* live inside the guts of nematodes that invade insects. The bacteria are released from the nematode, kill the insect, and set up rounds of bactreial and nematode reproduction[22]. Another microorganism for biological control is *Baculovirus anticarsia* used against the soybean pest *Anticarsia gemmatalis*[23]. The *Baculovirus* is a pathogen that attacks insects and other arthropods. They are extremely small and composed primarily of double-stranded DNA that codes for genes needed for virus establishment and reproduction. The majority of *Baculoviruses* used as biological control agents of in the genus *Nucleopolyhedrovirus.* These viruses are excellent candidates for specific, narrow spectrum insecticidal applications[24]. They have been shown to have negative impacts on plants, mammals, birds, fish and even on non-target insects. *Nosema locustae* is a microscopic protozoan used in several products to control grasshoppers[25]. Some of the fungi are available for pest control of cochroaches and the nematode *Steinernema feltiae* for flea control[26].

Antibiotics

Avermectins, a group of antibiotics isolated from the fermentation products of *Streptomyces avermitilis,* have insecticidal, acaricidal, and antihelminthic properties[5]. Abamectin is the common name assigned to Avermectin®, a mixture of avermectins containing 80 % avermectin B1a and 20 % B1b, homologs that have about equal biological activity[27]. Abamectin has certain local systemic qualities, killing mites on a leaf's underside when only the upper surface is treated.

Avermectins block the neurotransmitter α-amino butyric acid (GABA) at the neuromuscular junction in insects and mites. Visible activity, such as feeding and egg laying, stops shortly after exposure, though death may not occur for several days[5].

Transgenic-plant pesticides

As a result of advances in plant molecular biology, transgenic plants are becoming an attractive alternative to microbial systems for the production of proteins, carbohydrates, and lipids. They are potentially one of the most economical systems for large-scale production of recombinant proteins for industrial, pharmaceutical, veterinary, and agricultural uses[28]. Transgenic-plants are produced from genetic material added to the plants and can help in reducing the use of broad-spectrum insecticides, which have the potential to distrupt crop production by upsetting predator/pest ratios and creating secondary pest outbreaks[14]. Transgenic plants are also more target-pest specific and the amount of damage done to non-target organisms is eliminated[29]. These plants have been developed by scientists, often using genes from wild varieties with inbuilt disease resistance[30].

Scientists have had more success in engineering trees to control weeds and insects that plague tree plantations. The Oregon State University Tree Genetic Engineering Research Cooperative has engineered hybrid poplars to resist the herbicide glycophosphate and produce insecticidal Bacillus thuringiensis toxins[31,32]. In another study, Scottish Crop Research Institute Scientists found that ladybugs fed aphids reared on transgenic potatoes had reproductive problems and failed to live as long as ladybugs fed aphids from ordinary potatoes. The potatoes were engineered to produce insecticidal lectins, which are proteins from the snowdrop plant that bind to the surface of insect cells causing them to clump and stop functioning. In a greenhouse test, the transgenic plants remarkably reduced potato aphids, a serious pest of the crop, compared whit aphids on non-transgenic potatoes[31].

Nowadays, many crop-growers are switching to transgenic varieties to fight increasing weed and insect problems. For instance, insect-resistant cotton lines have been genetically altered to deter pests such as like pink bollworm. Other transgenic cottons are herbicide-resistant, allowing growers to spray weeds without killing cotton[33].

The Colorado potato beetle (CPB) has developed resistance to most insecticides. Transgenic potatoes are the varieties that contain genes for production of toxic proteins of *Bacillus thuringiensis* (Bt). In laboratory studies, some researchers examined CPB mortality on transgenic and non-transgenic potatoes. Bt-resistant larvae showed 86.7, 46.2, 10.0, and 14.0 % mortality for first, second, third, and fourth instar larvae held four days on transgenic plants. Bt susceptible larvae showed 100, 97.8, 58.3, and 48.3 % mortality for instars one through four, respectively[34]. Also, females held on transgenic plants did not lay eggs. The tomato is a practical example since it is one of the first transgenic crops. The transgenic-tomato made by Bt gene develops resistance against insects. The research on screening the possible toxicity of Bt protein indicate that Bt protein in concentrations up to 4000 times the maximum likely to be ingested (1 kg tomatoes per day) by man has no harmful effect on growth, blood cells, or on the gastro-intestinal tracts of mice after exposure for 28 days[35,36].

Pheromone-based pesticides

Pheromone is a chemical substance that is produced by an animal and serves especially as a stimulus to other individuals of the same species for one or more behavioral responses[37-39]. They are also called "ectohormones". Pheromones are usually volatile molecules. They could easily disperse into the environment. The functions of pheromones varies, though the sex attractants are the most well-known[40]. For decades, scientists have been studying pheromones and various applications have been discovered for them. Pest control is one of the major applications of insect sex pheromones. Pheromone traps play an important role in succesful integrated pest management programs. The traps utilize pheromone lures to monitor the presence of specific insect pests[41]. These traps are typically plastic nets or containers placed in or near any crop field and baited with a chemical attractant, pheromone. The pheromones used are chemicals that female insects excrete to attract male ones. Therefore, only male insects are caught in the traps[42].

Giving some examples of the use of pheromone technology, forestry researchers at Oregon State University have tested and proven a strategy to control Douglas-fir bark beetles using one or more pheromones to attrack or repel this serious forest pest. This repellant pheromone now only awaits approval by the Environmental Protection Agency (EPA)[43]. The papaya fruit fly, *Toxotrypana curvicauda*, is a major pest of commercial papaya worldwide. A previous research found that a green sphere coated with sticky material and baited with pheromone was effective in trapping male and female papaya fruit fly[44].

The fire ant is an agricultural and medical pest in the Southern and Southeastern United States. Its painful sting, aggressive behavior and large numbers have allowed it to dominate the native ant fauna and create a negative effect on the ecology of infested areas. In a study, the use of fire ant worker attractant pheromones to enhance the effects of currently available bait toxicants was investigated and used a worker attractive component of the queen recognition pheromone, invictolide was used to test the effectiveness of pheromone-enhanced baits. The results demonstrated that pheromone-enhanced baits are discovered significantly faster than non-enhanced bait[45,46].

The green bollworm, *Helicoverpa armigera*, a devastating pest, has assumed serious proportions recently in cotton growing in India. Hence, field experiments were conducted in cotton growing tracts in and around Coimbatore and traps with black rubber septa containing one milligram of a sex pheromone were used. The results indicated that the pheromone traps effectively attracts the moths for up to 15 days and there is a considerable reduction in moth catches[47].

Pheromone trapping-systems are also effectively used against some insects such as Southern pine beetle, *Dendroctonus frontalis,* German cockroach, leafrollers, oriental fruit moth, some species of Sesiidae such as *Synanthedon culiciformis, S. sphec-iformis, Chamaesphecia tenthrediniformis,* and *C. empiformis,* codling moth, *Cydia pomonella* which is an apple pest, corn earworm moth, black cutworm, and grape berry moth, *Endopiza vitana* in different parts of the world[48-56].

The phytopathogenic fungus *Ustilago hordei* was found to produce farnesylated peptides that act as mating pheromones. Efforts to purify the mating-type pheromone led to the discovery of a compound which was inhibitory to mating[57]. Another interesting example is the formicine ant *Camponotus consobrinus* which uses its hindgut to produce scent trails, and adds some poison gland secretions to excite its fellow workers to pursue it. Formicine ants secrete toxic formic acid from their poison glands and a study has shown that ant poison gland secretions in high concentrations repel stowaway beetles[58].

Plant-derived pesticides

Due to the environmental and toxic concerns of synthetic pesticides, there has been renewed interest in the search for natural sources of pesticides. Especially plant-derived pesticides, unlike synthetics, break down rapidly when exposed to heat, light, and water. Therefore, they are biodegradable, and this is an advantage over the synthetic ones[59].

They are processed into various forms including:
- preparations of crude plant material
- plant extracts or resin
- pure chemicals isolated from plants

Plant-derived pesticides are classified into seven groups:

-Nicotine and nornicotine
-Pyrethrum
-Rotenone
-Sabadilla
-Ryania
-Essential oils and terpenoids
-Neem

Nicotine and nornicotine

Nicotine and nornicotine are pyridine derivative alkaloids obtained from tobacco leaves, *Nicotiana tabacum*, and other *Nicotiana species. N. rustica* is the chief commercial source[13]. They have been used for their insecticidal properties since the middle of the 18th century. Nicotine is effective against most types of insect pests, but is used particularly for soft-bodied insects such as aphids and caterpillars[60]. Insecticidal formulations generally contain nicotine in the form of 40 % liquid concentrate nicotine sulfate and are currently imported by the U.S.A. in small quantities from India[25]. Nicotine breaks down rapidly in uv light and LD_{50} is 50 mg/kg[16].

Nicotine has an excellent contact activity, due to its ability to penetrate the integument of insects. This property increases the hazards of handling nicotine, as its contact toxicity to mammals is also significant. Nicotine mimics acetylcholine at the neuromuscular junction in mammals, and results in twitching, convulsions, and death, all in rapid order. In insects the same action is observed, but only in the central nervous system ganglia[60].

Pyrethrum and pyrethrins

Pyrethrum is the powdered dried flower head of the Pyrethrum daisy, *Chrysanthemum cinerariaefolium.* Most of the World's Pyrethrum crop is grown in Kenya, Tanzania, Equador and Tasmania. Pyrethrins refer to the six related insecticidal terpenoid compounds (cinerin I, II, and III, jasmolin I and II, pyrethrin I and II) that naturally occur in the crude material[61-63]. Pyrethroids are synthetic compounds derived from natural pyrethrins[25,64]. When pyrethrins are combined with a synergist such as piperonyl butyroxide, its killing power for insects increases dramatically. The United States Department of Agriculture (USDA) has stated that synergized pyrethrum is probably the safest of all insecticides for use in food plants[65].

Pyrethrins act by blocking nerve impulse transmission in both the peripheral and cental nervous systems of insects. Pyrethrum initially stimulates nerve cells to produce repetitive discharges, leading eventually to paralysis[60]. Immediate effects caused by Pyrethrins are skin irritation, asthmatic reactions, numbness of lips and tongue, vomiting, diarrhea, headache, uncoordination, stupor[66]. Pyrethrins and the synergists are biodegradable and rapidly disintegrate in sunlight and air. They are highly toxic to fish and bees[65]. LD_{50} value for pyrethrins is 2500 mg/kg.

Rotenone

The roots of *Lonchocarpus* species in South America, *Derris* and *Tephrosia* species in Asia, and several other related tropical legumes contain rotenone, a commercial insecticide found in the 1930s. Rotenone is a flavonoid derivative that strongly inhibits mitochondrial respiration[13]. It is a respiratory enzyme inhibitor, acting between NAD^+ and Coenzyme Q, resulting in failure of the respiratory functions in insects[60]. Immediate effects when exposed are numbness of mouth and tongue, nausea, vomiting, gastric pain, muscle tremors, uncoordination, irritation of skin and respiratory tract[66]. Since rotenone is extremely toxic to swine and fish, it is a selective pesticide used to reclaim lakes for game fishing[16]. LD_{50} of rotenone is 132 mg/kg.

Sab*adilla*

Sabadilla is an extract obtained from the ripe seeds of *Schoenocaulon officinale*, a tropical lily plant which grows in Central and South America[25]. The insecticidal activity of Sabadilla comes from the alkaloid fraction, which constitutes 3-6 % of the extract. The two most important compounds are the lipophilic alkaloids veratridine and cevadine, with veratridine having greater insecticidal potency. Sabbadilla rapidly breaks down in sunlight[60]. Immediate effects of poisoning by Sabadilla are irritation on to the upper respiratory tract and skin, vomiting, headache, giddiness, weakness, twitching, convulsions, hypothermia, death due to respiratory or cardiovascular failure[66]. Sabadilla extract is much less toxic to mammals than most other insecticides and is therefore safe to use.

The mode of action of the *Veratrum* alkaloids is similar to that of pyrethroids. When applied to a nerve, veratridin causes an increase in the duration of action potential, repetitive firing, and a depolarization of the nerve membrane potential, due to effects on the sodium channel. Veratridine prolongs the open state of the sodium channel by delaying channel shutting and by increasing the probability of channel opening[60]. LD_{50} value for Sabadilla is 5.000 mg/kg.

Ryania

Ryania, the water-soluble plant extract, has been used as an insecticide for about 50 years and consists of the powdered woody stems of *Ryania speciosa*, a South American shrub[25]. The extract contains several structurally related ryanoids, including ryanodine, 10-(O-methyl)-ryanodine, 9,21-dehydroryanodine, and ryanodol. The most toxic and abundant compounds in the extract are ryanodine and 9,21-dehydroryanodine, which are responsible for the insecticidal activity. The extract has a low acute toxicity to mammals[60]. Immediate effects observed by the ryania toxicity are retraction of eyes into socket, vomiting, weakness, diarrhea, slow deep breathing, salivation, central nervous system depression, coma, and death due to respiratory failure[66].

Ryanodine induces paralysis in insects and vertebrates by causing a sustained contracture of skeletal muscle without depolarizing the muscle membrane. A number of studies have confirmed that ryanodine can irreversibly activate the calcium release channel in the sarcoplasmic reticulum. The irreversible activation of this calcium channel floods the muscle fibers with calcium, inducing the sustained contraction of skeletal muscle and paralysis[60]. LD_{50} for ryanodine is 1200 mg/kg.

Essential oils and terpenoids

Folk medicines have traditionally provided insigths into promising sources of insecticides. Some of the most common essential oils used as insecticides are the oils of Cedar, Lavender, Eucalyptus, Pennyroyal, Rose, Geranium, Thyme, Wintergreen, Clove, Cassia, Anise, Bergamot, Pine tar, and Citronel[25,59]. Common natural biochemicals produced by these plants as insecticides include 1,8-cineole, citronellal, eugenol, α-pinene, and β-pinene. A derivative of the terpenoid allelochemical 1,8-cineole, with the common name of cinmethylin, is being commercially developed. Another plant terpenoid, camphene, was a very succesful herbicide in its polyhalogenated form. It was sold as a herbicide and insecticide, but was removed from the market in 1982 by the EPA. Other terpenoids of the lemonoid group from the families Meliaceae and Rutaceae containing plants rich in essential oils are potent growth inhibitors of several insect species[13]. Lamiaceae family also consists of many essential oil-containing plant species such as *Rosmarinus officinalis, Mentha pulegium, Ocimum basilicum, Salvia officinalis,* and *Lavandula species*[63,67]. The sesquiterpenoid lactone, artemisinin from *Artemisia annua (Asteraceae),* was found to inhibit plant growth and known as an ingredient of cinmethylin, the commercial herbicide[13].

Limonene or d-limonene is one of the terpenoids showing pesticidal activity. Extracted from *Citrus* peel, it is effective against all external pests in pets, including fleas, lice, mites, and ticks. It is virtually non-toxic to warm-blooded animals. Several insecticidal substances occur in *Citrus* oil, but most important is limonene, which constitutes about 98 % of the orange peel by weight. Its mode of action is similar to that of Pyrethrum. It affects the sensory nerves of the peripheral nervous system[25,60].

Neem (Margosa)

Neem products are derived from the Neem tree, *Azadirachta indica,* that grows in arid tropical and subtropical regions of south Asia and Africa[25]. The seeds and leaves of the neem tree are the source of a new class of pesticide. The main mode of action is an anti-feedant. Insect pests usually refuse to eat any plant covered with Neem and do so until they starve to death. Other actions are as a repellent and a reducer of an insectís ability to reproduce. Neem extracts tested by the Malaria Institute were found to repel the mosquito that causes malaria for up to twelve hours. Neem provides protection from not only mosquitoes, but also from biting flies, sand fleas and ticks. Because of Neemís proven effectiveness, insect repellents made with Neem are being used in malaria prone tropical countries. Neem is non-toxic to animals and people and is a biodegradable product. Only insects that eat plants are affected by Neem, leaving honeybees and other beneficial insects essentially unharmed[68,69].

The most active insecticidal compound found in Neem is azadirachtin, a nortriterpenoid belonging to the lemonoids. Azadirachtin causes insects to refuse to eat plants sprayed with neem. It has also shown some rather sensational insecticidal, fungicidal, and bactericidal properties, including insect growth regulating qualities[70]. As important as azadirachtin is, Neem's true effectiveness comes from the interaction of all of the compounds which affect different aspects of an insect's life. The mode of action of azadirachtin is that it distrupts molting by inhibiting biosynthesis or metabolism of ecdysone, the juvenile moulting hormone[60].

The number and complexity of Neem compounds which affects insects are highly unlikely for insects to develop resistance to Neem, which is a big problem in the case of synthetic insecticides against that more and more insects are developing resistance[67,68].

CONCLUSION

Terrestrial and marine organisms have an enormous potential for providing compounds with chemical diversity for the development of pesticidal agents as an alternative to the synthetic compounds. For this purpose, we have screened Turkish medicinal plants for their activity against agricultural pests and we have found that plants of Lamiaceae and Asteraceae families possess quite high pesticidal activites[71,72]. Our work is still in progress.

It is also possible to discover new and selective pesticidal agents using structure-activity relationships. Despite their value to agriculture, pesticides have also become direct and indirect threats to the health of humans and to the environment around the world. Therefore, development of new biopesticides with less adverse effects is imperative for a quality environment and survival of humankind.

REFERENCES

1. Johnson JM, Ware GW. *Pesticide Litigation Manual,* Clarck Boardman Callaghan, New York, 8th edition, 816-818, 1998.
2. Thomson WT. *Agricultural Chemicals,* Vol.I, *Insecticides,* Thomson Publications, Fresno, California, pp. 278, 1994.
3. Thomson WT. *Agricultural Chemicals,* Vol. II, *Miscellaneous Agricultural Chemicals,* Thomson Publications, Fresno, California, pp. 209, 1995.
4. Tomlin C (ed.). *The Pesticide Manual,* British Crop Protection Council, Blackwell Scientific Publications, Cambridge, pp. 1341, 1994.
5. Ware G. *The Pesticide Book,* 4th edition, Thomson Publications, Fresno, California, pp. 386, 1994.
6. Weinzierl R, Henn T. *Alternatives in Insect Management: Biological and Biorational Approaches,* North Central Regional Extension Publication No. 401. Cooperative Extension Service, University of Illinois at Urbana, Champaign, 1991.
7. Debach P, Rosen D. *Biological Control by Natural Enemies,* Cambridge University Press, New York, 202-207, 1991.
8. Bloomquist JR. Toxicology, Mode of Action and Target, Site-Mediated Resistance to Insecticides Acting on Chloride Channels, *Comp. Biochem. Physiol.,* 106C, 301-314, 1993.
9. Bloomquist JR. Neuroreceptor Mechanisms in Pyrethroid Mode of Action and Resistance, *Rev. Pestic. Tox.,* 2, 185-226, 1993.
10. Bloomquist JR. Ion Channels as Targets for Insecticides, *Ann. Rev. Entomol.,* 41, 163-190, 1996.
11. Clarck JM, Scott JG, Campos F, Bloomquist JR. Resistance to Avermectins: Extent, Mechanisms and Management Implications, *Ann. Rev. Entomol.,* 40, 1-30, 1995.
12. Coats JR (ed.). *Insecticide Mode of Action,* Academic Press, New York, 35-42, 1982.
13. Gill SS, Cowles EA, Pietrantonio PV. The Mode of Action of *Bacillus thuringiensis* endotoxins, *Ann. Rev. Entomol.,* 37, 615-636, 1992.
14. Hollingshaus J. Inhibiton of Mitochondrial Electron Transport by Hydramethylnon: A New Amidinohyrazone Insecticide, *Pestic. Biochem. Physiol.,* 27, 61-70, 1987.
15. Hollingworth R., Ahmadsahib K, Gedelhak G, McLaughlin J. New Inhibitors of Complex I of the Mitochondrial Electron Transport Chain with Activity as Pesticides, *Biochem. Soc. Trans.* (London), 22, 230-233, 1994.
16. Matsumura F. *Toxicology of Insecticides,* 2nd edition, Plenum Press, New York, 1985.
17. Meister RT. *Farm Chemicals Handbook,* Meister Publishing Co., Willoughby, 1993.
18. Mullins JW. Imidacloprid: A New Nitroguanidine Insecticide, ACS Symposium Ser. 524: Newer Pest Control Agents and Technology with Reduced Environmental Impact, 1993.
19. Nijhout FH. *Insect Hormones,* Princeton University Press, Princeton, 1994.
20. Ware GW. *Complete Guide to Pest Control,* 2nd edition, Thompson Publications, Fresno, California, 1998.
21. Duke SO. *Natural Pesticides from Plants,* In: Advances in New Crops, Janick J, Simon J, (eds.), Timber Press, Portland, 511-517, 1990.
22. Arnason T, Towers GHN, Philogene BJR, Lambert JDH. The Role of Natural Photosensitizers in Plant Resistance to Insects, *Amer. Chem. Soc. Symp. Ser.,* 208, 139-151, 1983.
23. Duke SO. Biosynthesis of Phenolic Compounds-Chemical Manipulation in Higher Plants, *Amer. Chem. Soc. Symp. Ser.,* 268, 113-131, 1985.
24. Duke SO. Naturally Occurring Chemical Compounds as Herbicides, *Rev. Weed Sci.,* 2, 15-44, 1986.
25. Duke SO. *Microbial Phytotoxins as Herbicides-A Perspective,* In: *The Science of Allelopathy,* Putnam AR, Tang CS, (eds.), New York, 287-304, 1986.
26. Duke SO, Lydon J. Herbicides from Natural Compounds, *Weed Technol.,* 1, 122-128, 1987.
27. Duke SO, Paul RN, Lee SM, Terpenoids from the Genus Artemisia on Potential Pesticides, *Amer. Chem. Soc. Symp. Ser.,* 380, 318-334, 1988.
28. Duke SO, Vaughn KC, Croom EM Jr, Elsohly HN. Artemisinin, A Constituent of Annual Wormwood (Artemisia annua), A Selective Phytotoxin, *Weed Sci.,* 35, 499-505, 1987.
29. Grainage M, Ahmed S. *Handbook of Plants with Pest-Control Properties,* Wiley-Interscience, New york, 1988.
30. Green MB, Hartley GS, West TF. *Chemicals for Crop Improvement and Pest Management,* Pergamon Press, New York, 110-116, 1987.
31. Jacobson M. The Neem Tree: A Natural Resistance Par Excellence, *Amer. Chem. Soc. Symp. Ser.,* 296, 220-232, 1986.
32. Klocke JA. Natural Plant Compounds Useful in Insect Control, *Amer. Chem. Soc. Symp. Ser.,* 330, 396-415, 1987.

33. Lydon J, Duke SO. Porhyrin Synthesis is Required for Photobleaching Activity of p-Nitrosubstituted Diphenyl Ether Herbicides, *Pestic. Biochem., Physiol.*, 31, 74-83, 1988.
34. Lydon J, Duke SO. Pesticide Effects on Secondary Metabolism of Higher Plants, *Pestic. Sci.*, 25, 361-373, 1989.
35. Lydon J, Duke SO. *Potential of Plants for Pesticide Use. Herbs, Spices and Medicinal Plants: Recent Advances in Botany, Horticulture and Pharmacology,* Vol.IV, Oryx Press, Phoenix, 1-40, 1989.
36. McLaren JS. Biologically Active Substances from Higher Plants: Status and Future Potential, *Pestic. Sci.*, 17, 559-578, 1986.
37. Mandava NB (ed.). *Handbook of Natural Pesticides. Methods,* Vol. I, *Theory,* Practice and Detection, CRC Press, Boca raton, 1985.
38. Rebeiz CA, Juvik JA, Rebeiz CC. Porphyric Insecticides. 1. Concept and Phenomology, *Pestic. Biochem. Physiol.*, 30, 11-27, 1988.
39. Rebeiz CA, Montazaer-Zouhoor A, Hopen HJ, Wu SM. Photodynamic Herbicides. 1. Concept and Phenomology, *Enzyme Microb. Technol.*, 6, 390-401, 1984.
40. Rice EL. *Pest Control with Nature's Chemicals,* University of Oklahoma Press, Norman, 25-34, 1983.
41. Rice EL. *Allelopathy,* 2nd edition, Academic Press, New York, 5-8, 1984.
42. Russell GG. Phytochemical Resources for Crop Protection, *New Zealand J. Technol.*, 2, 127-134, 1986.
43. Yang RZ, Tang CS. Plants Used for Pest Control in China, *Econ. Bot.*, 42, 376-406, 1988.
44. Mallet J. The Evaluation of Insecticide Resistance: Have the Insects Won?, *Trends in Ecology and Evaluation,* 4, 336-340, 1989.
45. Sparks TC. Insecticide Resistance and the Tobacco Budworm, *Rev. Pestic. Toxic.*, 2, 16-20, 1993.
46. Wierenga JM, Norris DL, Whalon ME. Stage-Spesific Mortality of Colorado Potato Beetle Feeding on Transgenic Potatoes, *J. Econ. Entomol.*, 89, 1047-1052, 1996.
47. Hayes WJ, Laws ER (eds.). *Handbook of Pesticide Toxicology, Classes of Pesticides,* Vol. III, Academic Press, Inc., New York, 56-89, 1990.
48. Lankas GR, Gordon LR. *Toxicology in Ivermectin and Abamectin,* Campbell WC, (ed.), Springer-Verlag, New York, 23-45, 1989.
48. Harding WC. Pesticide Profiles, Part 1: Insecticides and Miticides, *University of Maryland, Coop. Ext. Serv. Bull.*, pp.30, 1979.
49. Spitzer S. The WTO and Pesticide Reform, *Global Pesticide Campaigner,* 10, 6-11, 2000.
50. Cox C. 2,4-D: Human Exposure and Ecological Effects, *Global Pesticide Campaigner,* 10, 16-24, 2000.
51. Kegley S. California Remains Hooked on Poison, *Global Pesticide Campaigner,* 10, 3-5, 2000.
52. Reif JS. Companion Dogs as Sentinels for the Carcinogenic Effects of Pesticides, *Pesticides, People and Nature,* 1, 7-14, 1999.
53 Snoo GR, Schidegger NMI, de Jong FMW: Vertebrate Wildlife Incidents with Pesticides: A European Survey, *Pesticide Science,* 55, 47-54, 1999.
54. Naumann K. Influence of Chlorine Substituents on Biological Activity of Chemicals, *Pest Manage. Sci.*, 56, 3-21, 2000.
55. Halteren PV. Possible Consequences of An Internationally Agreed Pest Risk Assessment Scheme, *Bulletin OEPP/EPPO Bulletin,* 26, 545-547, 1996.
56. Steinrücken HCM, Hermann D. Speeding the Search for Crop Chemicals, *Chem. & Indust.*, 7, 246-249, 2000.
57. Abdel-Gawad MM, El-Sayed MM, Abdel-Hameed ES. Molluscicidal Steroidal Saponins and Lipid Content of Agave decipiens, *Fitoterapia,* 70, 371-381, 1999.
58. Khallouki F, Hmamouchi M, Younos C, Soulimani R, Bessiere JM, Essassi EM. Antibacterial and Molluscicidal Activities of the Essential Oil of the Chrysanthemum viscidehirtum, *Fitoterapia,* 71, 544-546, 2000.
59. Engvild KC. *Naturally Produced Organohalogens,* Grimwall A, de Leer EBW, (eds.), Kluwer, Dordrecht, 227, 1995.
60. Naumann K. *Synthetic Pyrethroid Insecticides, Structures and Properties,* Vol. IV, *Chemistry of Plant Protection,* Haug H, Hofmann H, (eds.), Springer, Heidelberg, 1990.
61. McKinlay KS, Brandt SA, Morse P, Ashford R. Droplet Size and Phytotoxicity of Herbicides, *Weed Sci.*, 20, 450-452, 1972.
62. Bromilow RH, Chamberlain K. Pathways and Mechanisms of Transport of Herbicides in Plants, in: *Target Sites for Herbicide Action,* Kirkwood RC, (ed.), Plenum Press, New York, pp. 245-284, 1991.
63. Jarvis NJ, Bergström LF, Brown CD. Pesticide Leaching Models and Their use for Management Purposes, in: *Environmental Behaviour of Agrochemicals,* Roberts TR, Kearney P, (eds.), John wiley & Sons, Chichester, pp.185-220, 1995.
64. Hubber R, Otto S. Bound Pesticide residues in plants, in: *Pesticide Chemistry: Human Welfare and Environment,* Vol. III, Miyamoto J, Kearney PC, (eds.), Pergamon Press, Oxford, pp. 357-362, 1983.
65. Loss MA. Phenoxyalkanoic Acids, in: *Herbicides: Chemistry, Degradation, and Mode of Action,* Vol. I, Kearney PC, Kaufmann DD, (eds.), Marcel Dekker, New York, pp. 1-128, 1975.
66. Harms HH. In vitro Systems for Studying Phytotoxicity and Metabolic Fate of Pesticides and xenobiotics in plants, *Pestic. Sci.*, 35, 277-281, 1992.
67. Zerba EN. Fumigant Canisters and Other Novel In-

secticide Delivery Systems for Public Health, *Public Health Magazine* (Bayer), 12, 62-71, 1995.

68. Bowers WS. Biorational Approaches for Insect Control, *Korean J. Appl. Entomol.*, 31, 289-303, 1992.
69. Cox AC, Balick MJ, The Ethnobotanical Approach to Drug Discovery, *Sci. Amer.*, 270, 82-87, 1994.
70. Bowers WS. Insecticidal Compounds from Plants, in: *Phytochemical Resources for Medicine and Agriculture*, Nigg HY, Deigler D, (eds.), American Chemical Society, Plenum Press, New York and London, pp. 227-235, 1992.
71. Bowers WS, Şener B, Evans PH, Bingöl F, Erdoğan İ. Activity of Turkish Medicinal Plants Against Mosquitoes *Aedes aegypti and Anopheles gambiae, Insect. Sci. Applic.*, 16, 339-342, 1995.
72. Şener B, Bingöl F, Erdoğan İ, Bowers PH, Evans PH. Biological Activities of Some Turkish Medicinal Plants, *Pure & Appl. Chem.*, 70, 403-406, 1998.