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# Naturally occurring molecules and synthetic analogues-status and prospect in view of biorational pest management*

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## INTRODUCTION

I am grateful to the Indian Mycological Society for giving me the honour to deliver this prestigious first S. B. Chattopadhyay Memorial lecture for the year 2006. I have chosen to speak on the topic entitled Naturally occurring molecules and synthetic analogues—status and prospect in view of biorational pest management. Biologically active natural products are derived from three major sources: the higher plants, fermentation of microorganisms and insects. However, the compounds derived from these sources may act within each or all of these domains. That is a compound derived from higher plants and microorganisms may affect insects, microorganisms and *vice versa*. Many plants exhibiting insecticidal properties have been known since time immemorial. It is only during the last 200 years that serious attempts have been made to unravel the chemical structures of the active principles occurring in many of the well-known plants having pesticidal properties. The significance of efficacy of secondary metabolites from natural sources utilized in Indian system of medicines /ayurvedic/ homoeopathy/ unani and in agriculture has been known to us since last many decades. Our ancestors are much more dependent on these type of natural products though in a very crude form for several decades. The primitive agriculture has also been very much dependent on natural resources based inputs and which has been practiced for many years.

With the advancement of civilization we are about to ignore our traditional resources, which could have been utilized in a more systematic manner for the development and sustainability of global ecosystem. The Agriculture sector dominates the economic scenario in our country and the occupation of nearly 60% population is in agriculture. Just to feed them all it will be necessary to grow as much food as possible. It is evident that land is a limiting factor in food production, therefore, improvement of agriculture with advance agricultural technologies have played a dominant role for much of the today's productivity. It has been found that the increasing trend of our food grain production is directly related with increasing trend of pesticides consumption/ other inputs in our country, thus revealing that chemical methods of pest control have served a potential role in increasing and sustaining productivity of our country. Since our independence, we are genuinely proud of the achievements in the Golden Jubilee Year (1997) of India's Independence and which may be engraved as the golden year of Indian agriculture. When India achieve an all time record of 199.32 M tonnes of food grain production. We have crossed 200 M tonne mark in the year 1999. Compared to 1950-51 productions of 51 M tonnes in 1997 food grain production is almost four fold larger. This has been possible due to intensification of agriculture/horticulture,which is a strategy to generate additional food and nutrition (Katyal *et al.*, 1999; Agnihotri *et al.*, 1999; Verma, 1998; Godfrey, 1995). Naturally year round cropping

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system will encourage more pests (insects, diseases due to pathogens, nematodes, weeds, rodents, birds etc.).Because of favorable growth and multiplication conditions offered by a tropical country like India, pests assume serious proportions throughout the year. It is, therefore, not surprising that losses due to pests are far greater in the tropics and semi-tropics than in the temperate regions of the world. Loss due to pests of various types is around 25-35%. Pest management is, therefore, a powerful strategy that can handsomely contribute to enhancement in crop productivity. Nevertheless, pest control with heavy dependence on treatment with pesticides is fought with dangers because of their harmful effect on environment and well being of man and animal. Although pesticides have become an integral part of modern/intensive agriculture, their excessive and non-judicious use has not only showing the potency of environmental pollution. But also developed resistance to several pests, caused pest resurgence and adversely affected beneficial organism like honeybee, pollinators and natural enemies like parasites and predators. To be environmentally benign, they should be biodegradable, capable of reducing the damage level and safe to fishes, bees, pollinators and other non-target organisms (Chowdhury *et al.*, 2002).

It is estimated that by the year 2010 about 20-30 per cent of the present day biorational agents will replace pesticides. However, pesticides will continue to remain as one of the main weapons in the hands of farmers to control pests, particularly weeds, nematodes and diseases. Keeping pace with the time, when environmental issues are agitating our minds, it should our endeavor to replace the conventional pesticides with safer products of synthetic, botanical or microbiological origin. Having taken cognizance of the hazards associated with obsolete pesticides, scientists throughout the world are engaged in looking for environment friendly pesticides that can provide safe and efficient crop protection options. In recent times number of break through has been occurred in respect of biopesticides with particular reference to botanicals, microbial pesticides, pheromones, IGR & new more promising crop protection agents. A glimpse of some of some of the natural bioactive molecules developed for agriculture may be presented (Chowdhury *et al.,* 2002) (Table 1).

**Table 1** : Intensity of pesticide consumption in different countries

| Country | Pesticide consumption (gm a.i/ha) |
|---|---|
| USA | 3000 |
| West Germany | 3000 |
| Mexico | 750 |
| Japan | 7000-9000 |
| Taiwan | 10000 |
| Korea | 6000 |
| India | 450-500 |

### *Indian Agriculture- Strengths, Richness of Biodiversity*

Tremendous natural biodiversity in crops, animals, insects, micro- organism available e.g. India accounts for 12% plants and 17% animal genetic resources of the globe. About 30,000 rice cultivars out of 1,20,000 are documented in the world cultivated. More than 1000 mango types are in field. Wide range of medicinal / aromatic plant (about 10,000) exists. Commercial cultivation of only a few giving 66 to 100 billion dollars annually. There are 32 breeds of cattle, 14 of buffaloes, 40 of sheeps, 20 of goats, 8 of horses and 6 of camels along with several types of other animals. 48,000 plants species and 89,000 biotic species ; marine species, birds, insects and micro organisms particularly saprophytes, insect species (Agnihotri *et al.*, 1999; Verma, 1998).

Natural products can be exploited in several ways in the discovery of new agricultural pest control agent. First they can be used as a crude extract for direct application to the crop. Alternatively, once purified, they can constitute the active ingredient of a formulated mixture or be used in admixture with a synthetic product.

When a natural product is insufficiently active in its own right, semi synthesis, or chemical modification, can, in principle, lead to derivatives with optimized properties. Such as improved level and spectrum of activity, reduced phytotoxicity, and increased photostability. Finally, as an extrapolation of the latter approach, the structure of a natural product can act as the source of inspiration for the pesticide chemist in the design of new totally synthetic products, which, to the untutored eye, may bear little resemblance to the original lead compound. The discovery of couple of remarkable pest control molecule viz: synthetic pyrethroids, carbonates, cartap etc are some of the examples (Heisey *et al.*, 1991; Swain and Downum, 1991; Godfrey, 1995).

The natural resistance of plants to herbivorous insects can often be explained by the presence of specific metabolites that acts as toxins or as behavior modifying agents. Oviposition deterrents can offer a first line of defense against insect pest and extracts of non-host plant have been effective in protecting otherwise susceptible hosts.

A search for active plant constituents that cause avoidance of treated plants for egg laying has led to examination of unacceptable plant species, which are closely related to preferred species.The cabbage butterfly, lays eggs on most members of cruciferae, but a few species such as Erysimum cheiranthoides are avoided. Potent oviposition deterrents have been isolated from this plant and characterized as cardenolides. Some marine algae and invertebrates produce growth regulator and feeding deterrents, active against terrestrial microorganismsThese resulted in development of antimicrobial, plant growth and insect control activity. Organic soluble fraction showed high level of insecticidal and antimicrobial activity while the aqueous fraction shows phytotoxicity.

## *INSECTICIDES*

### *Nicotine*

These compounds act as nerve poisons in both insects and mammals, but there is a great deal of variation in susceptibility among different species. Nicotine is obtained from the plants *Nicotiana tabacum* and *Nicotiana rustica* (Fam. Solanaceae) to the extent of 2-8%, but it also occurs in other plants. Nornicotine predominates in *Nicotiana sylvestris* and anabasine is extracted mainly from *Anabasis aphylla* (Chowdhury *et al.,* 2002).

### *Rotenone*

There are a group of compounds in the roots of *Derris* and other plants of the family Leguminosae which are similar to rotenone in chemical structure, such as deguelin, toxicarol, sumatrol, elliptone, malaccol, dalpanol, pachyrrhizone, dolincone, amorphin, munduserone, and esorone, collectively called rotenoids. However, retenone is the most important compound and insecticidal preparations of it have been used in crop protection since 1848.

The long slender roots are dried, ground to a powder, diluted with talc, pyrophyllite, clay, sulfur, or similar nonalkaline diluents and used as insecticide dusts containing 0.75 – 1.5% rotenone (Chowdhury *et al.,* 2002).

### *Pyrethrum*

Pyrethrum is one of the oldest organic insecticides known to man. Pyrethrin ( Fam. Compositae) from *Pyrethrum cinerarifolium sp* even today is competitive with many of the new generation insecticides for domestic use. This is principally due to its low toxicity to mammals, nonpersistency and high toxicity to insects coupled with its remarkable effectiveness in causing insect knockdown (Chowdhury *et al.,* 2002).

### *Terpenoids*

The liminoids or tetranortriterpenoids, of which azadirachtin is a member, represent the upper end of the array of plant-produced terpenoids which discourage predation by insects. At the lower end, such relatively simple monoterpenes as limonene and myrcene play a role in protecting plants that produce them. A number of polyhalogenated monoterpenes, isolated from marine algae, have demonstrated moderate insecticidal activities Pulegone-1,2-epoxide is reportedly the major insecticidal component of the medicinal plant *Lippia stoechadoifolia* (Chowdhury *et al.*, 2002).

### *Neem*

Its insect control efficacy was first recognized by the withstanding of neem trees from the locust, which swarmed on the tree, but left without feeding. The extracts from seeds and leaves have pest/insect control activities and extraction is easy. The leaves or seeds are merely crushed and steeped in water, alcohol, or other solvents. The extract contains 4 major and perhaps 20 minor active compounds and can be used without further refinement or the most effective ingredients can be isolated and formulated as commercial products (Chowdhury *et al.*, 2002).

The main neem chemical is a mixture of three or four related compounds. They belong to tetranortriterpenoid (limonoids) and which are the followings :

1. Azadirachtin(IV) : the main agent for trolling insects, representing 90% of the effect on the most pests; contents are usually 2-4 mg/g kernel. It is a feeding deterrent and growth regulator, repelling and disruptin the growth and reproduction of pests.
2. Meliantriol : a feeding inhibitor, causing insects to cease eating in extremely low concentrations.
3. Salannin : a powerful feeding inhibitor.
4. Nimbin and nimbidin : show antiviral activity.

   Others : Deacetylazadirachtin is as active as azadirachtin. Some neem compounds act as systemics. When exposed to sunlight, neem products degrade and lose their pest-control activities.

### *Terpenoids*

| Name (Family) | Plant species | Pesticidal use |
|---|---|---|
| Limonene (Rutaceae) | *Citrus aurantium* | Insecticidal |
| Gossypol (Malvacaeae) | *Gossypium hirsutum* | Larvicidal |
| Clerodendrin -A (Verbenaceae) | *Clerodendron tricolomum* | Antifeedant |
| Azadirachtin (Meliaceae) | *Azadirachta indica* (*Melia indica*) | Antifeedant and insect-growth regulator |

### *Alkaloid*

Recent work with extracts of *Delphinium* seeds, known to be insecticidal, has revealed that the major active toxin is methyl lycaconitine. Using a housefly head homogenate, methyllycaconitine was shown to be potent inhibitor of a - bungarotoxin. Based on the mehyllycaconitine finding, Pelletier and Ross undertook the preparation of a series of esters and ethers of structurally related alkaloids, i.e., delphisine, neoline, delphine, lycoctonine, aconitine, delphonine, and N-deacetyl appaconitine.There is recent report on the isolation of the alkaloids responsible for the antifeedant properties of Colorado larkspur (*Delphinium geriri*)

### *Neristoxin*

The compound 4-dimethylamino-1,2-dithiolane, now known as neristoxin, was isolated from the marine annelid *Lumbriconereis heteropoda*. Marenz in 1934, white flies were noted to die after feeding on dead bodies of the annelid. From the synthesis program, two compounds, the *bis*-amide and later the *bis*-benzensulfonyl derivative were developed for commercial application by the Takeda Chemical group. The amide, cartap, proved effective in the field on the rice stem borer (*Chilo suppressalis*) and a number of other insects. The benzenethiosul fonate, bensultap, is especially effective against the Colorado potato beetle (*Leptinotarsa decemlineata*). Both compounds proved less toxic to mice than neristoxin (Chowdhury *et al.*, 2002).

### *Sabadilla*

Sabadilla, long known for its insecticidal properties, is the dried powdered ripe seeds of *Schoencaulon officinale*, A. Gray (Fami Liliaceae) also known as *Sabadilla officinarum* and *Veratrum sabadilla* The major insecticidal components of sabadilla are veracevine,veratridine, the 3-veratroyl and cevadine, the 3-angenoyl esters of veracevine. Veratridine is one of several alkaloids, including aconitine and grayanotoxin, identified as neurotoxins that affect sodium ion channels in excitable membranes (Chowdhury *et al.*, 2002).

### *Ryania*

Considerable work has been accomplished in isolating, identifying, and establishing the relative insecticidal activities of the compounds of Ryania, the powder obtained by grinding the dried plant *Ryania speciosia* (Flacourtiaceae). Ryanodine and dehydroryanodine comprised over 80% of two ryania preparations analyzed and were among the most active of the componenets (Chowdhury *et al.*, 2002).

### *Stemofoline (Pyrrole)*

Extracts of the roots of Stemonaceae plants have was used for the control of agricultural insects in China. Stemofoline, an alkaloid isolated from the leaves and stems of *Stemona japonica*, has been found to be the major insecticidal component having a complex struc. When fed on artificial diet at 100 ppm to fourth instar silkworm larvae (*Bombyx mori*), there were immediate toxic symptoms and death within 24hr. Conversely, stemofoline was inactive at 100 ppm in artificial diet fed to cabbage armyworms (*Mamestra brassicae*) (Chowdhury *et al.*, 2002).

### *Pyrroles*

The compound dioxapyrrolomycin was isolated and identified from fermentation broths of *Streptomyces* strains in quick succession by three different groups. Dioxapyrolomycin represents one of a series of antibiotic halogen containing nitropyroles labeled pyrrolomycins. It is effective against the fallowing insects.

| Species | LC50 (ppm) |
|---|---|
| Southern armyworm (*Spodoptera eridania*) | 40 |
| Tobacco budworm (*Heliothis virescens*) | 32 |
| Two-spotted mite (*Tetranychus urticae*) | 10 |
| Western potato leafhopper (*Empoasca abrupta*) | >100 |

### *Unsaturated Amides*

The search by the Elliott group turned up 172 amides that fit their definition. Twenty-eight were reported to have at least a trace of insecticidal activity and, of these, 23 were isobutylamides and 5 were piperidides, e.g.; Pipericide.

### *Cyclodepsideptides*

Cyclodepsipeptides, are cyclic compounds in which the ring is composed of residues of amino and hydroxyls acids joined by amide and ester bonds. Many are antibiotics: a number have been recognized for their insecticidal properties. The destruxins are a series of cyclodepsipeptides consisting of five amino acids and an a - hydroxyacid, 17 destruxins have been identified from 3 different sources. The presence of what became the first of these materials, destruxins A and B, was reported in 1954 when the blood of silk worm larvae killed by the fungus Metarhizium anisopliae proved toxic when injected into helthy worms. Isolation of these two insecticidal compounds was described in 1961 and the structures were reported in 1964. Their isolation, structural identification, and synthesis of Isarin, destruxin have been reviewed.

### *Furanocoumarins*

The furanocoumarins are typically found in plants of families Rutaecae and Umbelliferae although their range is much wider. Armyworms are unable or unwilling to survive on wild parsnip, *Daucus carota* L. (Umbelliferae). This fact and the knowledge that wild parsnip contained the furanocoumarin xanthotoxin, known for its ability on light activation to react with pyrimidine bases in RNA and DNA, led to Berenbaum's experiment with armyworms. Unlike the armyworm, swalowtail butterfly larvae (*Papilio polyxenes*) can survive on wild parsnip because they are able to detoxify and xanthotoxin (Chowdhury *et al.*, 2002).

### *Polyacetylenes*

Most of the biological evaluation for these polyacetylene has been directed at a variety of microorganisms rather than toward insects. Many of the plant-produced biologically active acetylenic compounds do not require photoactivation. Falcarinone and falcarindiol, compounds characterristic of the Apiaceae and Araliaceae, are representative. Of interest, falcarindiol was isolated from the common carrot, *Daucus carota,* and in addition to being toxic to *Daphnia magnastrauss,* it was also quite toxic by injection to mice (Chowdhury *et al.*, 2002).

### *Terthienyl*

The nematicidal components of the roots of *Tagetes* (African merigold) were shown to be the stable crystalline a - terthienyl and the unstable oil, 5-(3-buten-1-ynyl)-2, 2-bithienyl. The presence of these compounds has been demonstrated in a large number of species within the genus Asteraceae. These thiophenes suppressed infection by the nematode *P. penetrans* (Chowdhury *et al.*, 2002).

### *Chromenes*

Chromenes (benzopyrans) and benzofurans of diverse structures are known from many species of higher plants but the majority occur in the Asteraceae. Their distribution and biological activities along with the structures of 167 isolated compounds has been reviewed. Outside of the precocenes, 6,7-dimethoxy-2, 2-dimethylchromene and 7-methoxy-2, 2-dimethylchromene, noted for their ability to induce precocious metam (Chowdhury *et al.*, 2002).

### *Mammeins*

The extensive work done on extracts of seeds of the evergreen tree *Mammea americana* (Fam. Guttiferae), long known to be insecticidal. The active component was isolated as a crystalline material comprised mostly of the coumarins like structure. These differed from the inactive compounds in the series by having an acetoxy group as substituent, where the others were unsubstituted. At the time of this discovery, the acetoxy coumarin surangin B was identified as an antibacterriaal agent from the roots of *Mammea longifola*. Surangin B was also shown to be insecticidal and confirmed the importance of the acetoxy group (Chowdhury *et al.*, 2002).

### *Domoic acid*

Domoic acid isolated from the seaweed *Chondria armata,* and to a lesser extent, a-kainic acid, from the seaweed *Digenea somplex,* exhibited insecticidal activity when injected into the American cockroach and when applied topically to the housefly and German cockroach (Chowdhury *et al.*, 2002). Orphisms in some insects by destroying the gland that secretes juvenile hormone, several other chromenes viz; encecaline have attracted attention as insecticides.

**Coumarins**

| Name | Plant species ( Family) | Insecticidal use |
|---|---|---|
| Erosin | *Pachyrrhizus erosus* (Leguminosae) | Insecticidal |
| Begapten | *Orixia japonica* | Antifeedant (Rutaceae) |
| Isopimpinellin | *O. japonica* (Rutaceae) | Antifeedant |

**Miscellaneous Compounds**

| Name | Plant species ( Family) | Insecticidal use |
|---|---|---|
| Myristicin | *Pastinaca sativa* (Umbelliferae) | Pyrethroid |
| Diallyl disulphide | *Aliium sativum* (Liliaceae) | Insecticidal |
| 2-Phenethyl isothiocyanate | *Brassica rapa* (Cruciferae) | Insecticidal |
| Fluroacetic acid | *Dichapetalum cymsus* (Chailletiaceae) | Insecticidal |
| Affinin | *Helipsis longipes* (Asteraceae) | Insecticidal |
| b-Asarone | *Brassica rapa* (Cruciferae) | Insecticidal |

### *Fungicides*

1. Natural products have played a significant role in the discovery of new fungicides and bactericides, either by their direct application to diseased or susceptible plants or through their exploitation in the design of analogs with optimized biological and physical properties.
2. The earliest recorded use of naturally derived fungicidal remedies has been attributed to agriculturists of ancient Rome, who used various plant extracts to ward off fungal infestations in their crops.
3. Use of discrete, uncharacterized natural products (i.e., single, purified compounds as opposed to mixtures and crude extracts) on a commercial scale, was a practice in earlier times.
4. Dating from the 1960s with the advent of compounds such as the antibiotic streptomycin. Natural products can be exploited in several ways in the discovery of new agricultural fungicides.
5. First , can be used as extracts for direct application,alternatively after purification.

More recently, with the increasing emphasis on intensive monoculture and the economic drive to maximize farmers' profits, the detrimental effects of fungal and bacteria on crops have gained in significance. Yield and quality lossess now represent an unacceptable penalty to farmers, who have turned to the use of chemicals in order to control diseases and guaranteed a satisfactory return on their investments. Fungicides and bactericides now form an important sector of the total agrochemical business, with worldwide sales in 1993-94 of approximately $4.8 billion, equivalent to 19% of the total agrochemical market. The use of fungicides has also been gradually increasing in our country.

***List of antifungal compounds occurring in higher plants***
***Phenolics and phenolic acids***

| Name of the compound | Plant (Family) | Antifungul activity against |
|---|---|---|
| Catechol | *Allium cepa* (Liliaceae) | *Colletotrichum circineus* |
| Pyrogallol | *Castenea sativa* (Fabaceae) | *Endothia parasitica* |
| 2-Methoxy hydroquinone | *Triticum aestivum,* *Hordeum vulgare* (Gramineae) | *Ustilago tritici* |
| p-Hydroxy benzoic acid | *Pyrus malus* (Rosaceae) | *Sclerotinia fructigena* |
| Pinosylvin | *Pinus sylvestris Lentinus lepideus, Coniofora puteana* (Pinaceae) | *Merulius lacrymans* |

***List of antifungal compounds occurring in higher plants***

**Flavonoids :**

| Name of the compound | Plant (Family) | Reported antifungul against |
|---|---|---|
| Phloretin | *Pyrus malus* (Rosaceae) | *Venturia inequalis* |
| Pinostrobin | *Cajanus cajan* (Leguminosae) | *Botrytis cinerea* |
| Flemichapparin | *Flemingla chapper* (Leguminosae) | *Rhizopus nigricans, Curvularia lunata,* |
| *Helminthosporium oryzae* | *Flemingla chapper* | *Alternaria solani C. lunata* |
| 2', 4'-Dihydroxy chalcone | (Leguminosae) | *Rh. nigricans* |

***List of antifungal compounds occurring in higher plants: Isoflavonoids, including coumestans and pterocarpan compound***

| Name of the compound | Plant (Family) | Antifungul activity against |
|---|---|---|
| Genistein | *Apios tuberosa* | *Helminthosporium* |
| 2'-Hydroxy genistein | *A..tuberosa* | *Helminthosporium* |
| Luteone | *Lupinus luteus* | *Cochliobolu* |
| Kievitone | *Vigna catjang* | *Rhizoctonia solani* |

***List of antifungal compounds occurring in higher plants: Steroids and Steroidal Alkaloids Reported***

| Name of the compound | Plant (Family) | Antifungul activity |
|---|---|---|
| Amasterol | *Amaranthus viridis* (Amaranthaceae) | *Helminthosporium* oryzae |
| Parillin | *Smilax aristolochiaefolia* (Liliaceae) | *Antifungal* |
| Tomaline | *Lycopersicon esculentum* (Solanaceae) | *Septoria lycopersici* |

Natural products have played a significant role in the discovery of new fungicides and bactericides, either by their direct application to diseased or susceptible plants or through their exploitation in the design of analogs with optimized biological and physical properties. The earliest recorded use of naturally derived fungicidal remedies has been attributed to agriculturists of ancient Rome, who used various plant extracts to wards off fungal infestations in their crops.

Natural products can be exploited in several ways in the discovery of new agricultural fungicides, in the following ways :

a. They can be used as a crude extract for direct application to the crop.
b. Alternatively, once purified, they can constitute the active ingredient of a formulated mixture.
c. Be used in admixture with a synthetic product. When a natural product is insufficiently active in its own right, semi synthesis,
d. Chemical modification, can in principle lead to derivatives with optimized properties, such as improved level and spectrum of activity, reduced phytotoxicity and increased photostability.

The antifungal/ bactericidal properties of those natural products that have been exploited commercially as fungicides and bactericides can be conveniently taken into two distinct classes of chemical compounds , the aminoglycosides [e.g., streptomycin , validamycin A ,and Kasugamycin , and the nucleosides [e.g., polyoxin B and D and blasticidin].

All of those compounds are manufactured by large-scale fermentation of different species of *Streptomyces*. Together they command less than 1% of the total fungicide market and are sold in only a handful of countries around the world. A further example of a nucleoside, mildiomycin, was registered for use as a treatment for powdery mildews but has not yet made a significant impact in the market place. Other structurally unrelated antibiotics, cycloheximide (actidione), cellocidin, and ezomycin A, have also been used as fungicides but are very minor products.A couple of them are presented now.

***Streptomycin***

Produced by the fermentation of *Streptomyces griseus,* first commercially used as systemic bactericides for the control of blight and wide variety of bacterial rots, cankers, and wilts in fruits, vegetables etc (Godfrey, 1995). The mode of action of Streptomycin is thought to be inhibition of aminoacyl-t RNA binding in the 70S ribosome complex. It is much more effective against Gram-positive species of bacteria than the Gram –negative bacteria. As with other aminioacylglycoside antibiotics, it has very low acute oral toxicity ($LD_{50}$- 10,000 mg/kg BW).

***Validamycin A***

Then second important chemical of this group of antibiotics. It occurs as mixtures of some closely related compounds as validamycin A to G, produced by the fermentation of *Streptomyces hygroscopica* (Godfrey, 1995). As a commercial antibiotic used as treatment of Rizoctonia diseases such as rice sheath blight, black scurf of potato and damping off of vegetables. It is formulated as soluble concenetrate at 30g/l and as dust for seed treatment at 3 g/kg. Its more of action is not clear, but it is known to decrease the maximum rate of hyphal extension and to increase hyphal branching without affecting the organism's specific growth rate.

***Kasugamycin***

First isolated from *S kasugaensis* and its structure were established. It is an aminiglycoside comprising a 1D-chiral-inositol moiety linked to the oxalamidine derivatives of kasugamine (Godfrey, 1995). Obtained by a large scale fermentation of *S kasugaensis* and sold in the name of Kasumin and Kasugamine as a systemic bacteriocide/fungicide for the control of diseases on rice especially rice blast *(Pyricularia grisea),* fruits, and vegetables. It is thought to be prevent protein synthesis by inhibiting initiation complex formation on both 30S and 70S ribosomal subunits. Acute oral $LD_{50}$ 22,000 mg/kg on rat.

***Polyoxins B and D***

These are closely related nucleosides bearing peptidic chain constituents at C-4 of the furanose ring. A total of 13 polyoxins have been isolated from fermentation of S.cacaoi but two have been found to be fungicidal.Polyoxin B and D differ in the oxidation state of the uracil component (Godfrey, 1995). Polyoxin B is effective for the control of variety of fungal infections of fruits and vegetables including alterneria in apple, Pears and grey mould on vine and tomatoes. Polyoxin D is effective on sheath blight of Rice. Both the chemicals is thought to disrupt cell wall biosynthesis by mimicking UDP-N-acetylglucosylmine, the natural substrates for the enzyme chitin synthesis. Neither of these compounds show high toxicity to mammal and fish.

The acute oral toxicity of the two compounds $LD_{50}$ 21,000 mg/kg and 9600 mg/kg

***Blasticidin S***

First isolated chemical from *S.giesochromogens*.The structure and absolute stereochemistry was established by chemical means and confirmation by x-ray crystallography (Godfrey, 1995). Two main structural components: Blastidic acid and cytosinine.It has been proved tht the compounds is bisymthesized from D-glucose, L-a-arginine, and L-methionine. It is being trade by the name Bla-s as contact fungicide with protectant and curative properties especially foe the control of *Pyricularia grisea* (rice blast) as foliar application. It is used commercially as benzylaminobenzenesulfonate salt to reduce phytotoxicity. Acute oral toxicity of the salt is 53.5 mg/kg for rats. More toxic than other chemicals of this group. Blasticidin S acts by binding to the 50S ribosomes in prokaryotes at the same site as gougerotin, thereby leading to inhibition of chain elongation.

***Mildiomycin***

Water soluble basic antibiotic produced by Streptoverticillium rimofaciens as B-98891.It is 5—hydroxymethylcytosine nucleoside isolated by adsorption and ion-exchange chromatography (Godfrey, 1995). It is a promising eradicant and some systemic activity against a number of powdery mildews (viz; *Sphaerorotheaca* spp, *Erysiphe* spp, *Psodosphaerae* spp, and *Uncinula* spp. It is having low toxicity towards plant (LC50- 40mg/L 7 LD50-599mg/kg. It thought to inhibit protein synthesis in fungi by blocking peptidyl-tranferase. There is an increasing emphasis on the use of natural products as the starting point for the synthesis of simpler synthetic or semisynthetic compounds with optimized biological, physical, and environmental properties, rather than for use in their own right. Because the semisynthetic approach relies heavily on the ready availability of sufficient quantities of the natural starting materials, as well as on the development of appropriate synthetic methodology, it is less attractive than the total synthetic of simplified analogs, provided that the latter is a feasible option.Recent examples or natural products that have been considered as leads for the discovery of new fungicides and that will be discussed in this section are pyrrolinitrin, the β-methoxyacrylates etc.

***Pyrrolnitrin***

Pyrrolnitrin was isolated from *Pseudomonas pyrrocinia* in 1964 by Arima and co-workers. This simple secondary metabolite has been of interest as a topical antifungal treatment for some years and is sold under the trade name Pyroace. The first indications of the potential of the natural products itself in agriculture appeared in a patent application filed in 1969. However, it soon became apparent that pyrrolnitrin was not sufficient stable in sunlight to give an acceptable effect in the field, and much of the recent work in this area has focused on the synthesis of analoges with greater photostability. Ciba has led the way and its work has so far produced two promising compounds; fenpiclonil (formerly CGA 142705) and CGA 173506, which is still in development (Godfrey, 1995).

***β-Methoxyacrylates***

A second and potentially more important class of natural products derived fungicides to emerge in the last decade are the b-methoxyacrylates, which have also been termed "strobilurin analogues". These synthetic compounds are formally derived from a family of fungicidal natural projects related to strobilurin and oudemansin. Strobilurin A shows significant levels of fungicidal activity towards a range of plant pathogenic fungi *in vitro* but not *in vivo*, owing to its photochemical instability and its relatively high volatility. The b-methoxyacrylates are to be found in the mycelia of several general of small basidiomycete fungi (*Strobilurus tenacellus* and *Oudemansiella mucida*) which grow on decaying wood, and 14 related compounds (11 strobilurins and 3 oudemansins) have been characterized to date (Godfrey, 1995).

***Thiolutin***

The natural product thiolutin and its homolog aureothricin were the first members of the pyrrothine family of antibiotics to be isolated from strains of *Streptomyces* over 40 years ago. Since then, nine further closely related analoges have been discovered which have shown interesting biological activity against a wide range of both gram-positive and gram-negative bacteria, as well as amoeboid parasites and pathogenic fungi, in particular, thiolutin has been effective against a number of agricultural pathogens, including black rot and fire blight on apples, tobacco blue mould, and wilt on tomatoes. Thiolutin is thought to act on nucleic acid metabolism at the RNA polymerase step. It has been reported to be a potent inhibitor of RNA chain elongation ($I_{50} = 2 \times 10^{-5}$ M) and its action is freely reversible (Godfrey, 1995).

A versatile synthesis of thiolutin, holomycin, and analogs was devised in order to determine the structural requirements for (and hence optimize) fungicidal activity. The synthetic route has been established and over 50 analoges, of type 26 were prepared (including the natural products aureothricin, isobutyropyrrothin, and xenorhabdin IV), representing a wide range of substitutents ($R^1$, $R^2$, $R^3$ = H, alkyl, alkenyl, aryl, aralkyl, etc.) attached to the pyrrothine nucleus. Many of these compounds showed fungicidal activity *in vivo* against a broad spectrum of commercially important fungal pathogens (*Plasmopara viticola, Phytophthora infestans, Cercospora arachidicola, Venturia inaequalis, Pyricularia grisea* and *Puccinia recondita*) at concentrations below 100 ppm. The best compounds showed good protectant activity against *Plasmopara viticola* at rates as low as 3 ppm.

- **A.** The development of new technologies with implication of pesticide discoveries including target site directed rational design, intensive screening, biotechnologies, genomics as challenged agricultural chemist and industry.
- In order to make a significant break through for the identification of new fungicide with noble mode of action and increased efficacy:
- Blind screening of available organic compounds has been replaced by the use of following specific criteria :
- Molecular size, b. Hydrophobicity, c. Ionic charge and d. Chemical class to pre select compound that are more likely to have agricultural utility
- Natural products also continued to be an increasingly a useful source for the discovery of bioactive lead compounds.
- **B.** Some of these noble type of compounds having noble mode of action and synthetic analogs are
- <u>Natural</u> — <u>Synthetic</u>
- Strobilurin group — Azoxystrobin
- 1.Strobilurin-A — Kresoxim-methyl
- 2.Odemansin
- Activity: Inhibitors of mitochondrial electron transport cytochrome bc complex III. Broad spectrum activity with a site specific fungicide also least to a significant increase in the potential for disruptive resistance.
- <u>Natural</u> — <u>Synthetic</u>
- 3.Antimycin A — Cyazofamid, Dimefluazole
- Activity: Specific inhibitor of Oomycete fungi(*Phytophthora, Pythium* etc.)
- <u>Natural</u> — <u>Synthetic</u>
- Phenyl pyrrole group
- Pyrrolnitrin — Fenpiclonil, Fludioxonia
- Activity: Use for the control of *Botrytis cinerea* etc
- Cause intercellular accumulation of polyols,
- a consequence of inhibition of protein involved osmoregulation

*Some of the research works carried out by the scientist of our group on Naturally occurring pesticides*

**A.**1. In search of naturally occurring insect control agent from plant sources, we have been able to isolate/ characterized couple of compounds from different plants sources. A diterpene hydroquinone from *Clerodendrom siphonenthus* has been isolated/ characterized and found to be perfect feeding deterrent.

2. Further, amorpholone, a rotenoid insecticide was also isolated and characterized from the plant *Tephrosia candida* and found to be very much efective against *S. itiura*
3. Some of the crude and finer fractions of some of the plants have been found to be very much effective as insect control and disease control agent.

Prumycin(str) 4-D-alanylamino-2-amino-2,4-dide-oxyl-L-arabinoseidscivered by random screening methods inhibited limited number of phytopathogenic fungi *viz; Botrytis cinerea, Pyricularia grisea and S. cinerea.*These compound are effective in green house trials for protection of peach from infection by a gray mould., *B.cinerea.*

Irumamycin(str) is 18memberd macolide with a neutral sugar moiety.

It is active *in vitro* against filamentous fungi phytopathogens such as *P. grisea, B.cinerea, S. cinerea and Altrenaria kikuchiana.*

Both these compound are metabolized probably totye sugar and the aglucons moieties. Both of which are far less active. Attempts are being made for chemical modification and microbiological transformation for commercial utilization.

**B.**1. Since simple coumarins are reported by antifungal, we carried out chemical and biological investigations on *Selenium tenui-folium* (Fam. : Umbelliferae). A number of furocoumarins could be isolated from this plant which were found to be good inhibitors against *Helminthosporium oryzae.*

2. The structure activity relationships of the furocoumarins isolated from *S. tenuifolium* against *H. oryzae* suggested that imperatorin and geranyloxy sporalen having side chains at 8-position possessed some effects in increasing fungitoxicity

3. Alkoxy (Xantholoxin) and hydroxyl (Xantholoxol) groups at C-8 position also showed fungitoxic activity.

4. However, no significant effects were observed by furocoumarins having alkoxy and prenyloxy side chains at C-5 position.

5. Furtheremore, fungitoxicity decreased when C-8 prenyloxy side chain was oxygenated or the double bond of the same was hydrated (Heraclenin and Heraclenol)

6. Xantotoxol and 8-geranyloxypsoralen found to be most effective in the germination inhibition test against *H. oryzae.*

**C.**1. The plant *Flemingia chapper* (Fam. : Leguminousae) is known to possess medicinal and antifungal properties.

2. Three antifungal compunds 2',4' – dihydroxychalcone, flemichapparin and flemichapparin – A having unusual aromatic substitution pattern could be isolated from *F. chapper* .

3. Again, isoflavonoids including coumestans and pterocarpans are considered to play a major role in the natural disease resistance of plants.

4. Interestingly, flemichapparin – B, a new pterocarpan and flemichapparin – C, a new coumestan occurring in the roots of *F. chappar* showed 50% growth inhibitory activity against *H. oryzae* and *Alternaria solani* at a concentration of 70 ppm.

**D.**1. The leaves of Didymocarpus pedicellata(Fam. : Gesnariaceae) keep well on storage and are not attacked by fungi in humid atmosphere.

2. Two new flavanones, Didymocarpin, Didymocarpin – A and a new flavone-pediflavone and a new chalcone-Isodidymocarpin along with some known chalcones and quinochalcone occurring in *D. pedicellata.*

3. These compounds were found to possess both antifungal (against *H. oryzae, Fusarium oxysporum,* etc.) and antibacterial (against *Xanthomonas campestries)* activity at concentrations ranging from 50 – 250 ppm.

4. Phytochemicals investigation of yet another species *D. aurentiaca* led to the isolation of two new chalcones, Aurentiacin and Aurentiacin – A as well as two a- pyrone derivatives, 5,6-dehydrokawain and 7,8-epoxy-5,6-dehydrokawain. These also found to posses fungitoxic activity.

Promising biocides including botanicals in use commercially and under development for biorational pest management are described below.

***Insecticide***

1. Neem and neem based formulation
2. Azadirachtin based formulation
3. Terpenoid like pulegone-1,2- epoxide from *Lippia stoechaboifolia*
4. Nereistoxin from marine annelid- cartap hydrochloride
5. Stemofoline, extracts (alkaloid) of roots of stemonacae plants as insecticide
6. Unsaturated amides – pipericide, insecticidal activity
7. Terthienyl – alpha terthienyl, from tagetis (African merigold), effective against nematodes

**Fungicide**

1. Blasticidin S – from *S. griseochromogenes* against rice blast
2. Kasugamycin – isolated form *S. kasugaensis,* amino glucoside having an inositol moiety, effective against diseases of rice, fruits and vegetables
3. Polyoxin B – it is a closely related nucleoside bearing peptide chain and a furan ring, isolated from *S. cacaoi,* effective against diseases.

**Herbicide**

1. Phosphinothricylanylalanin – discoverd from *S. hygroscopicus,* effective against broad spectrum post immergence herbicidal activity
2. Trialaphos – it is tripeptide related with previous compound also isolated from fermentation broth and its derivatives can be used as herbicide.
3. Cycloheximide – it is a microbial product, lot of promise as herbicide.

## CONCLUSIONS

Despite the obvious attractions of using natural products in agriculture, particularly at a time of great public concern about man-made pesticides they still make up a vanishingly small proportion (<1%) of the global market for fungicides and bactericides. β-methoxyacrylates appear to have a much more promising future.Furthermore, there are concerns, particularly among the more advanced countries in the world, that the widespread use of antibiotics in agriculture might lead to the creation of resistant strains, which could limit the efficacy of medical treatments for human. In contrast, commercial products derived from natural products (such as pyrrolnitrin). In the absence of new outlets for existing products, it seems likely t9hat the natural products currently in the marketplace will be progressively replaced by more effective natural and synthetic compounds that can offer advantages in terms of cost-efficacy, resistance-breaking potential, and environmental safety.

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