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Insecticides from Fermentation Secondary Metabolites 【Review article】

微生物第二代謝物開發為殺蟲劑的展望【綜合論述】

Eddie Hang Chio*
招　衡*

*通訊作者E-mail : eddiechio@yahoo.com

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Abstract

Microorganisms produce a number of novel and useful molecules including insecticides. Avermectin and spinosad are fermentation secondary metabolites with excellent insecticidal activities with combined sales over US$ 1.25 B. Both products are classified under the category of Agricultural Antibiotics although they post very weak to no antimicrobial activities. By nature, they should be classified as bio-insecticides. ROC government has committed to biopesticides research since 1995 and their focuses were on Bt-based products, a primary metabolites from fermentation. There is no screening operation as yet for insecticides from fermentation secondary metabolites on the island. Chance, serendipity and luck played a critical role in the discovery of avermectin and spinosad. The serendipity aspect in the spinosad discovery has never been published and will be discussed here.

摘要

微生物發酵所產生的第二代謝物非常多樣化，其中不乏具有殺蟲效果的化學結構，亞弗素及賜諾殺是兩個傑出的發酵代謝物殺蟲藥。該兩產品總年銷額高達12.5億美元。台灣百泰生技的〝台灣寶〞與賜諾殺同為微生物第二代謝物。台灣寶列為生物農藥，而亞弗素及賜諾殺目前歸類於農用抗生素，這種歸類有待探討，因為這兩種藥只有殺蟲性而沒有殺菌的效果。

台灣早於1995年選定生物農藥為重點研究項目，並繼續推出生物農藥產品，諸如昆蟲費洛蒙、線蟲、微生物殺菌劑及蘇力菌等產品。但這些生物農藥市場相對於微生物第二代謝物殺蟲藥的市場是微乎其微，而微生物發酵第二代謝物殺蟲劑的研發，在台灣尚未展開。亞弗素及賜諾殺的發現是團隊努力加上運氣的結果，本文為首次公開發表如何幸運地研發出賜諾殺的過程。

Key words: Fermentation secondary metabolites, avermectin, spinosad, discovery
關鍵詞: 發酵第二代謝物、亞弗素、賜諾殺、研發。

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Insecticides from Fermentation Secondary Metabolites

Eddie Hang Chio* Visiting Specialist, Department of Entomology, National Taiwan University, Taipei, Taiwan

ABSTRACT

Microorganisms produce a number of novel and useful molecules including insecticides. Avermectin and spinosad are fermentation secondary metabolites with excellent insecticidal activities with combined sales over US$ 1.25 B. Both products are classified under the category of Agricultural Antibiotics although they post very weak to no antimicrobial activities. By nature, they should be classified as bio-insecticides. ROC government has committed to biopesticides research since 1995 and their focuses were on Bt-based products, a primary metabolites from fermentation. There is no screening operation as yet for insecticides from fermentation secondary metabolites on the island. Chance, serendipity and luck played a critical role in the discovery of avermectin and spinosad. The serendipity aspect in the spinosad discovery has never been published and will be discussed here.

Key words: Fermentation secondary metabolites, avermectin, spinosad, discovery

Introduction

Mother Nature has provided alternatives to existing chemicals both in the short and long term (Rodgers, 1993; Starnes *et al*., 1993). The discovery of penicillin in 1929 ushered the beginning of the "golden age" of natural products research. Over 40% of the drugs approved in the last 20 years are derived from natural products. While it is well documented that natural products, especially fermentation secondary metabolites, offer vast and unlimited sources of useful molecules for both pharmaceuticals and agricultural usage, the lion's share of the screening efforts are dedicated to finding pharmaceuticals. This effort has lead to the discovery of approximately 6,000 pharmaceutically active natural products from microorganisms as compared to only a handful of structures for insect pest control (Omura, 1986). However, out of these few structures, two insecticides have proven to be extremely successful with combined annual sales over US$ 1.25 B. (Temple and Smith, 1994; Thompson *et al*., 2000). Avermectin is from the microbe *Streptomyces avermitilis,* and spinosad is from the microbe, *Saccharopolyspora spinosa*. Outside of these two successes, we have only scratched the surface in terms of discovering useful molecules from Mother Nature.

ROC government committed to make

*Correspondence address
e-mail: eddiechio@yahoo.com

biopesticides one of their five major biotech research focuses in 1995. Since then many biopesticides have been launched in Taiwan such as the azadirachtin, (plant extracts), *Bacillus subtilis* and *B. thuringeinsis* (microbial fungicide and insecticide respectively). But plant extracts and microbial fungicides have a very limited market. *Bacillus thuringiensis* based products account for about 43% of the total Taiwan biopesticides market with around NT$ 30 M (< US$ 1 M) (Agbio, 2004). For reference, the global market for Bt-based products is around US$ 220 M or approximately 90% of the bio-pesticides market. In other words, Taiwan's biopesticides have a lot of room to grow. It is worth mentioning that there are hundreds of researchers and manufacturers working on Bt-related projects (McDougall, 2001). Although the fermentation secondary metabolites based products account for a significant bigger biopesticides market, there is no research on insecticide discovery from fermentation secondary metabolites in Taiwan. Insecticide research and development is considered a long term investment and a high rish/ high reward business. Fermentation secondary metabolite based products have a significantly bigger market than other types of biopesticides and with only two molecules to compete with, it makes good business sense to refocus our biopesticide discovery research efforts on fermentation secondary metabolites.

The discoveries of both avermectin and spinosad are a combination of hard work, smart work and luck. Their discoveries are remarkable and may be considered serendipitous to some degree. Although chance does not produce drugs, the role played by chance should be recognized and welcomed. As you may recall, sildenafil citrate was originally developed for heart diseases, but was eventually marketed for sexual dysfunction, and became Viagra, one of the best-recognized products in the world. While the "lucky accident" aspects in the avermectin discovery have been covered (Campbell, 2005), the serendipitous results of the spinosad discovery have never been mentioned. As one of the inventors of spinosad, and the one who designed the unique screen that led to its discovery, I would like to share the details surrounding spinosad's discovery with you.

My ultimate wish for this article is to jump-start discussion and increase interest in insecticides from fermentation secondary metabolites in Taiwan.

Definition of secondary metabolites

It is important to point out that products from fermentation could be from primary metabolites or secondary metabolites. *B. thuringiensis* based products are considered primary metabolites while avermectin, spinosad and most of the antibiotics are from the secondary metabolites. According to the microbiology dictionary, the secondary metabolites are organic compounds that are not directly involved in the normal growth, development or reproduction of organisms. The function or importance of these compounds to the organism is usually of an ecological nature as they are used as defenses against predators, parasites and diseases. Penicillin is a good example of the secondary metabolites from *Penicillium chrysogenum*. The main scope of our discussion here is on the secondary metabolites.

Definition of agricultural antibiotics

Around 40% of all antibiotics are from fermentation. (Omura, 1986). Secondary metabolites of certain bacteria and fungi could be lethal to other bacteria, fungi or insects. For example, Penicillin is produced by *P. chrysogenum*, kills many gram positive germs and is therefore known as the "wonder" drug (Harvey and Mason,

1998). Antibiotics also played a significant role in the food-animal industries especially when animals are raised in a confined environment. A simple infection could wipe out all animals on a farm. Adding antibiotics to the feed keeps the animals healthy. Farmers later noticed that antibiotics also significantly promoted animal growth. Nowadays, approximately 90% of these naturally fermented antibiotics are sold as feed additive (Lucas, 1972). The antibiotics used in animals are called agricultural antibiotics or antibiotic insecticides. The most successful "agricultural antibiotic" for worm and insect control is ivermectin with annual sales over US$ 1 B. (Hwang *et al.*, 2003). While avermectin-based products have exceptional potency and breadth of spectrum against roundworms and arthropod parasites, its germ killing power is too weak to be considered as an antibiotic. Another significant agricultural antibiotic is spinosad with annual sales over US$ 250 M (Willinger, 2000). This product kills a wide range of insect pests but shows no antimicrobial activity at all.

Antibiotic residue in farm animals has been linked to antibiotic resistance in humans, and as a result, many agricultural antibiotics have been banned as feed additives in Europe, USA and Asia (Thorp and Cargill, 1999). The term "agricultural antibiotic" has become a target for environmentalists. These two well-known fermentation secondary metabolites show strong anti-worms and anti-insects activities but no anti-germs activity. They should not be classification as agriculture antibiotics. By nature, they should be classified as bio-insecticides. For example, the microbial fungicide, Bio-Bac from Taiwan's Bion Tech, is a secondary metabolites from *B. subtilis*. This microbial fungicide is registered and marketed as a bio-pesticides in Taiwan (Bion Tech Inc. website). Better classification may be needed for this type of bio-insecticide should we decide to promote our research in this area.

Brief product descriptions of avermectin and spinosad

There are other insecticidal secondary metabolites on the market or in development (e.g. milbmycin, jietacin, polynactins, pyrrolomycins), but their market shares are very minor (<<1%) when compared to avermectin and spinosad. Therefore, the scope of our discussion will be focused on these two major products.

Avermectin

Avermectin (Avid®, Agrimek®) is the most successful natural product pesticide (sold by Merck to Novartis). It is a purified natural product compound with a complex structure (Fig. 1), produced in fermentation by the microbe, *Streptomyces avermitilis*. It controls mites, leafminers, and cockroaches. A second generation product, emamectin, with improved caterpillar activity, is being launched by Novartis.

Temple and Smith (1994) did a good job in summarizing the activity of Avermectin. See reference for details.

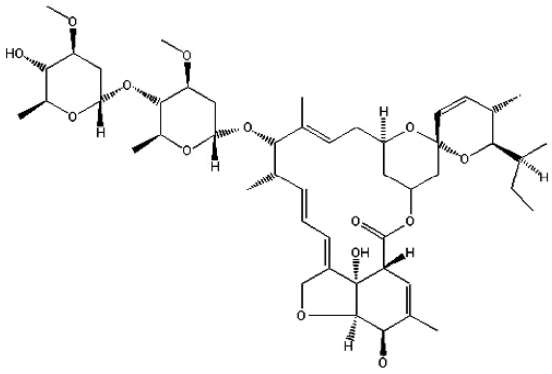

Fig. 1. Structure of avermectin.

Spinosad

Dow Agrosciences has launched spinosad (structure shown in Fig. 2), a metabolite

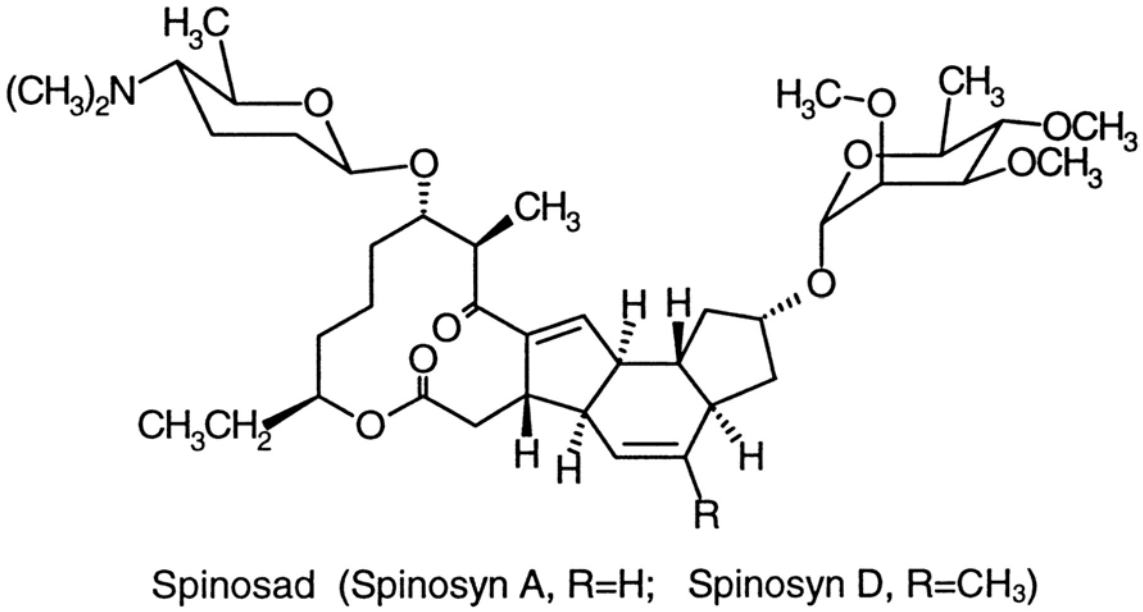

Fig. 2. Structure of spinosad (spinosyn A, R=H; spinosyn D, R=CH3).

from *Saccharopolyspora spinosa*. Spinosad is the first active ingredient proposed for a new class of insect control products, the naturalytes. Spinosad has been developed to provide rapid control of Lepidoptera and other pests with minimum disruption of beneficial insects and other non-target organisms. Due to its high efficacy and selectivity, it becomes a good partner in many Integrated Pest Management Programs. Spinosad has been registered under the US EPA's reduced risk program. Spinosad products are now registered on over 150 crops in more than 30 countries. It has an excellent toxicological and environmental profile. Due to its high selectivity against pests and good margin of safety to non-target species, spinosad won US-EPA Presidential Green Chemistry Challenge Award in 1999. Dow AgroSciences also promises a series of similar naturalyte products. Summary of spinosads activity see Thompson, *et al*., 2000.

The business aspects in bioinsecticide R/D

In the past 50 years, control of insect pests has relied almost exclusively on the use of synthetic chemicals pesticides. The use pattern was driven by the introduction of new and often more effective chemicals classes of broad spectrum insecticides (Floate *et al*., 2001). The introduction of these new classes of pesticides was due largely to the development of insect pests with resistance to those insecticides. More applications of the same type of insecticides only facilitated the speed of resistance. In addition, the emergence of the secondary insect pests became an increasing problem because of the elimination of beneficial insects that traditionally kept the secondary pests in check. From the end-user standpoint, environmental and health risks associated with those broad spectrum insecticides became increasingly apparent. This has spurred the search for more environmentally

sustainable insect control options. Many scientists believe that bioinsecticides are an undoubtedly better alternative to their synthetic counterparts (Millman, 2005). Many bioinsecticides have demonstrated promising results in insect pest control directly or played a role in the Integrated Pest Management programs. Products such as insect hormones, insect pheromones, insect growth inhibitors, *B. thuringiensis*-based products, insect virus based products, insect parasitoids, insect predators, nematodes, protozoa, and fungi are some examples of biopesticides. Like drugs, bioinsecticides take time, resources and money to develop. The cost of research and development for a bioinsecticide, be it an insect hormone, nematode, Bt-based products or fermentation metabolites, was estimated to be US$ 25-100 M back in 1998 (Broadhurst, 1998). With inflation and higher regulatory standards today, the cost for biopesticides should be higher now. Biopesticide is niche market with less than 2.5% of the total insecticide market (Imhoff, 2005). From a practicality standpoint, we need to focus our R/D efforts on the major segment within this niche market. The market size for biopesticide however is not easy to come up with due to the ambiguity of the definition of biopesticides, and the dynamic nature of the biopesticide market. Ramarethinam's report (2006) listed the biopesticide market ranging from US$ 60 to US$ 600 with the average of US$ 221 M (Table 1). The highest estimation however is US$ 1 B but that figure includes market for crops with Bt-genes (Imhoff, 2005). Therefore, this figure is excluded from our discussion.

These market figures, however, do not include the sale figures of two bioinsecticides from fermentation metabolites, the avermectin-based products and the spinosad-based products. By their natures, these two agriculture antibiotics are members of the biopesticides family. They are natural products, no difference from the plant extracts, *B. thuringiensis* based products or *B. subtilis* based products. The avermectin-based products have reached US$ 1 B in 2003 (Hwang *et al.*, 2003) while Spinosad-based product's annual sales were estimated at US$ 250 M (Willinger, 2000). Simple math shows that the combined market for biopesticides; US$ 221 M (90% Bt based product) and these two fermentation metabolites (US$ 1.25 B) would be US$ 1.471 B. Therefore, in reality, these two fermentation metabolites account for 85% of the biopesticide market.

While pyrethroid-based products used to be considered bioinsecticide, with market worth US$ 1.3 B (Auriga Industries report, 2006), the majority of the pyrethroid-based products nowadays are manufactured by chemical synthesis, and are therefore no longer classified as natural products (The FPT Committee on Pest Management and Pesticides, 2002). For this reason, these are also excluded from our discussion.

Considering the fact that fermentation secondary metabolites have 85% of the biopesticide market with only two major structures to compete with, focusing our efforts on fermentation metabolites research makes good business sense. For comparison, Bt based products in Taiwan accounted for approximately NT$ 13 M in 2004, while spinosad was NT$ 22 M. In addition, Bt market is a very crowded field with hundreds of manufacturers. For example, Taiwan alone has over 200 pesticide importers and 50 manufacturers and most of them are more or less working on Bt-based products (Agbio, 2004).

Chance, serendipity and luck in spinosad's discovery

Louis Pasteur once said, "In the field of observation, chance favors only the prepared mind". Serendipity, in various shades and forms, has played a significant role in drug discovery. We may be on the threshold of a new era of rational drug

Table 1. Biopesticides market size

Company	Year	Market size ($ M)	Remark
Abbott	1994-5	60	
Ecogen	1994-5	60	
Mycogen	1994-5	60	
Sandoz	1994-5	60	
BMP	1994-5	70	
Freedonia	1997	150	US only
Novartis	1997	194	
Market Intelligence	1998	196	
Business Communication	1997	197	US only
Ernst and Young	1995	312	
Woodburn	1998	410	
BASF	1997	500	
Agrow	2000	600	
Average		221	

design, but most medications for infectious diseases have arisen, and continue to arise, from chance observation. The role played by chance should be recognized and welcomed. Luck is another form of serendipity in discovery. Lewis Thomas, the former President of the Memorial Sloan-Kettering Cancer Center stated, "I'm not as fond of the notion of serendipity as I used to be. It seems to me now that as you get research going... things are bound to begin happening if you've got your wits about you. You create the lucky accidents."

I established a new insecticide screen protocol for fermentation broths at Eli Lilly and discovered spinosad back in the early 80's. It was a remarkable discovery, a true story about team work, hard work, smart work and luck: a very important part of the spinosad's success never mentioned in other spinosad publications. Here are a few issues related to serendipity associated with the spinosad discovery.

A simple modification enabled us to detect spinosad activity

As do many other laboratories, we followed the World Health Organization guidelines and used the yellow-fever mosquito larvae (*Aedes aegypti*) as insecticide activity indicator. (Christophers, 1960). The guideline calls for using the 4^{th} instar larvae as indicator. Twenty-five 4^{th} instar larvae are countered and put in a large mouth Mason jar with 300 mL of water containing a known amount of insecticides. Their LC50 values are calculated 24 hours post treatment. However, this WHO standard procedure was not suitable for our high thought-put screen operation. To fit the automated format, we pipetted larvae into the 96-well microtiter plate containing fermentation samples and used the Minimum Inhibition Concentration measurement to evaluate the insecticidal effects of the fermentation samples. The head of the 4^{th} instar larva was too big for our special pipette; therefore, the 3^{rd} instar larvae were used instead. This simple change increased the assay detection limit from approximately 5 PPM to 0.25 PPM, a 20 fold increase in sensitivity. This change enabled us to detect spinosad at less than 1 part per million levels. The initial concentration of spinosad in fermentation broth was

about 1 part per million. Should we have used the 4th instar larvae as indicator; we could have missed the spinosad.

Rare species of Actinomycetes produce novel structures that are not necessarily active. But it was.

To address the dereplication issue, microbiologists started picking rare species of Actinomycetes in hopes of finding novel structures from rare species. However, there is no guarantee that a novel structure is an active structure. Only three species of *Saccharopolyspora* were reported when spinosad was discovered (Mertz and Yao, 1990).

- *S. erythraea*: producer of erythormycin, tylosin.
- *S. hirsuta*: not produce any metabolites of interest.
- *S. spinosa*: selective insecticides.

We are lucky that this novel structure from the rare species happens to be very active against insect pests.

Saccharopolyspora spinosa produces a serial of metabolites, the two major metabolites happens to be the most active factors:

Spinosad is mainly a mixture of spinosyns A and D (thus its name, spinosAD). When those factors were evaluated individually against mosquitoes, factors A and D were the most active ones (Fig. 3. Chio, 1986). Field trials data on other pests confirmed our early laboratory evaluations that factors A and D are the two most active factors (Thompson *et al.*, 2000). If the most active factors were the minor factors, then more development time would be needed to work on strain selection and strain improvement. This would have been a hurdle in our product decision.

Spinosad is selective against major insect pests

After spinosad activity was detected by yellow-fever mosquito, it was tested against other economically-important pests. Current data shows that it is highly active on insects including species from the orders Lepidoptera, Diptera, Hymenoptera, Thysanoptera, and a few Coleoptera, but not active at all for other orders (Thompson *et al.*, 2000). Those insect pests that are susceptible to spinosad, happen to be economically-important (Broadhurst, 1998). If its selectivity had been more inclined toward minor insect pests, then it would have been another hurdle in our product decision.

Spinosad is environmental friendly

There is no guarantee that active fermentation metabolites are environmentally friendly; we always hope for the best. Spinosad turned out to be so safe to the environment and non-target species that it won the US EPA Presidential Green Chemistry Challenge Award (EPA, 1999). Its unique mode of action on the nicotinic acetylcholine receptors and on the GABA receptor may partly explain its high potency against chemical resistant insects and its low toxicity toward mammals. However, we don't have a good explanation about its low toxicity against most of the non-targeted insect species. Its outstanding safety profile was far beyond our expectations.

Spinosad is unique

After spinosad was discovered, we screened the original soil sample again but could not find another *Saccharopolyspora*. We then collected more soil samples from the original spot where the *Saccharopolyspora spinosa* was found and soil from the vicinity. We used the improved fermentation technologies to increase the odds of finding the *Saccharopolyspora* species and applied the most sensitive assay to detect spinosad or related structures. Unfortunately, we were unable to find another *Saccharopolyspora spinosa*. Lilly shut down their insecticide screen program

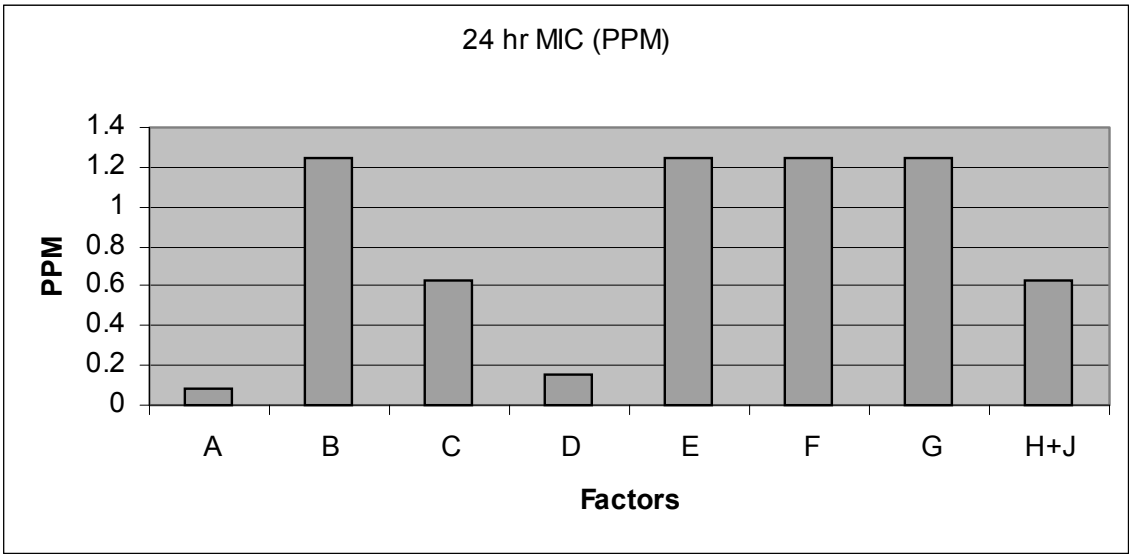

Fig. 3. The effects of spinosad factors on *Aedes aegypti*.

one year after spinosad was discovered. So far, spinosad is still the only product of its kind on the market.

Prospecting

The combined sales of avermectin and spinosad have reached US$ 1.25 B, or 85% of the total bioinsecticide market if they are put under the proper classification. These two fermentation metabolites confirm our belief that Mother Nature offers vast and unlimited sources of useful molecules. The discovery of both avermectin and spinosad may be considered serendipitous to some degree. With proper screening operation system in place, certainly there are more molecules like avermectin and spinosad to be found. Taiwan committed to biopesticides in 1995 and several biopesticides have been launched in Taiwan since then. But so far there is no project in bio-insecticide from fermentation secondary metabolites. A proper screening operation system for bio-pesticides should include microbiologist, biologists and chemists. There are many outstanding microbiologists, biologists, and chemists in Taiwan. However, they are not working together as a team for bio-pesticides. From the practicality standpoint, the ROC government may want to consider forming such team in fermentation secondary metabolites research.

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It is my great honor to come back to the Department of Entomology as a Visiting Specialist after graduating from this Department in 1970. I thank Prof. Chiou-Nan Chen for initiating the invitation and Prof. How-Jing Lee and his committee for forwarding my case to the National Science Council for their final approval (NSC 96-2811-B-002-003). I also would like to thank Prof. En-Cheng Yang for encouraging me to write this article.

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微生物第二代謝物開發爲殺蟲劑的展望

招　衡* 台灣大學昆蟲學系客座專家　台北市羅斯福路四段 1 號

摘　　要

微生物發酵所產生的第二代謝物非常多樣化，其中不乏具有殺蟲效果的化學結構，亞弗素及賜諾殺是兩個傑出的發酵代謝物殺蟲藥。該兩產品總年銷額高達 12.5 億美元。台灣百泰生技的〝台灣寶〞與賜諾殺同爲微生物第二代謝物。台灣寶列爲生物農藥，而亞弗素及賜諾殺目前歸類於農用抗生素，這種歸類有待探討，因爲這兩種藥只有殺蟲性而沒有殺菌的效果。

台灣早於 1995 年選定生物農藥爲重點研究項目，並繼續推出生物農藥產品，諸如昆蟲費洛蒙、線蟲、微生物殺菌劑及蘇力菌等產品。但這些生物農藥市場相對於微生物第二代謝物殺蟲藥的市場是微乎其微，而微生物發酵第二代謝物殺蟲劑的研發，在台灣尚未展開。亞弗素及賜諾殺的發現是團隊努力加上運氣的結果，本文爲首次公開發表如何幸運地研發出賜諾殺的過程。

關鍵詞：發酵第二代謝物、亞弗素、賜諾殺、研發。

*論文聯繫人
e-mail: eddiechio@yahoo.com