I. Introduction

Even though their fungal nature may not have been recognised as such, fungi growing on insects or their larvae have long drawn the interest of naturalists. Prominent examples are *Cordyceps* species and the silkworm diseases, white and green muscardine, caused by *Beauveria bassiana* and *Metarhizium anisopliae*. Even today these fungi and their interactions with their hosts are still a matter of investigations. A modern pictorial overview on entomopathogenic fungi is given by Samson et al. (1988). Fungal diseases are dealt with by Carruthers and Soper (1987) and the underlying biochemistry and molecular biology have been described by Khachatourians (Chap. 17, vol. VI) and others.

*Cordyceps sinensis* as well as *B. bassiana*-infected silkworms have a long tradition as drugs in Japan and China. *C. sinensis* (caterpillar mush- room) is still highly sought after and is sold on Asian markets as a remedy against all kinds of illnesses. It is used as a decoction (tea) prepared from dried fruit bodies, including the caterpillars (larvae of the sphinx moth, *Hepialus armoricanus*) on which the fungus grows. Powders obtained by grinding the fungus and larval bodies are added to the diet or the whole thing is cooked with chicken or duck. Yet another method of enjoying it are alcoholic extracts (Pegler et al. 1994). It is found at high altitudes in the Himalayan regions of China, Tibet and Nepal (Tang and Eisenbrand 1992). Mycelial extracts obtained from submerged cultures have been reported to exhibit similar beneficial activities, like anti-tumour, antisenescence, hypolipidemic, anti-arterosclerotic, anti-inflammatory, sexual function-restorative, immune system enhancing and stress reducing (Zhu et al. 1998a,b). The components, except some rather weak cytotoxic sterols from mycelia (Bok et al. 1999), responsible for most of the curing activities, however, have not yet been identified – quite contrary to the insecticidal toxins of entomopathogenic fungi, which have been intensively investigated for more than 40 years. Especially from cultures of *M. anisopliae* and *B. bassiana*, more than 30 depsipeptides have been reported, most of which exhibit insecticidal activities (Chapman and Hall 1999; Berdy 2000).

Lately, due to environmental damage caused by synthetic insecticides and due to the problem of emerging resistance towards many insecticides, natural products have come back into focus and are considered to be the ultimate choice for new products. In addition, natural bioactive metabolites might lead to new targets. Along with plants, fungi have been found to provide a good source for new insecticides.

In spite of the isolation of numerous insecticidal metabolites, fungal secondary metabolism has only lately been considered as a source for nematicidal compounds. This seems astonishing since the first report on fungi with a predacious mode of living dates back to Zopf (1888).
nematophagous fungus to be described was *Arthrobotrys oligospora* Fres. by Fresenius in 1852. The ability to capture nematodes was demonstrated by Zopf and later by Drechsler who added many other nematophagous fungi to the list (Duddington 1960). Taxonomic descriptions and revisions of nematophagous fungi have been carried out by Barron (1977), de Hoog (1985), van Oorschot (1985) and Rubner (1996).

In the first part of this chapter, insecticidal metabolites from fungi and the potential of the metabolites as plant protectants will be addressed. The second part deals with nematicidal metabolites from fungal sources. This part focuses on compounds described since 1996; the literature before 1996 has been recently reviewed by Anke and Sterner (1997). For a review on plant-derived nematicides see Chitwood (1993). Readers interested in the potential of fungi as biological control agents are referred to Roberts and Hajek (1992), Milner and Staples (1996), Malsam et al. (1997), and Jansson et al. (1997).

II. Insect Diseases Caused by Fungi and the Toxins Involved

*Beauveria bassiana* and *Metarhizium anisopliae* are not only the first fungi to be recognised as insect pathogens, but they are also the species of which the secondary metabolism has been most intensely investigated. The main insecticidal class of metabolites isolated from these fungi as well as from *Aschersonia* species are the destruxins, cyclic depsipeptides. More than 30 destruxin-like compounds have been isolated to date and semisynthetic ones have been prepared (Dumas et al. 1994; Krasnoff et al. 1996; Jegorov et al. 1998; Chapman and Hall 1999; Berdy 2000). Structurally related depsipeptides are the isarolids, isariins, beauveriolids, bassianoloid, beauvericins and enniatins. In Table 1, the compounds, the producing fungi, most of which are insect pathogens, as well as some of the biological activities, are summarised. For several enniatins, in addition to the activities listed in the table, an interaction with the GABA_A receptor in rat brain has been reported (Bergendorff et al. 1994). The structures of a few typical metabolites presented in Table 1 are shown in Fig. 1. Besides the insecticidal activities, which are rather moderate, these compounds exhibit a range of other biological effects, and are therefore not suitable as lead compounds for new selective insecticides. Beauvericin, originally isolated from *B. bassiana*, has in recent years become classified as an important mycotoxin, produced by many *Fusarium* species (Gupta et al. 1991b; Logriece et al. 1998). Mycotoxins are defined by their toxic activity towards humans and livestock as well as their occurrence in food and feed-stuff. For a review see Betina (1989). The role of enniatins and beauvericins in fungus-plant interactions and their biosynthesis has been addressed earlier in this series by Hohn (see Chap. 7, vol. V, Part A).

*Hirsutella thompsonii* produces an insecticidal protein, but no low molecular metabolites have been reported so far. From *Entomophaga*, *Erynia*, *Conidiobolus* (see below) *Lagenidium*, *Nomuraea*, *Akanthomyces*, or *Harposporium* species no metabolites are known, whereas from *Cordyceps* species several metabolites have been reported but none of them affects insects. Compounds from *Cordyceps*-related anamorphs like *Isaria*, are listed in Table 1.

*Tolypocladium cylindrosporum*, a pathogen of mosquito larvae, and *Beauveria nivea* are among the many fungi which produce cyclosporins. For cyclosporin A, an important clinical immunosuppressant (Schreier 1997; see also Chap. 7, this vol.), insecticidal and anthelmintic properties have been described (Weiser and Matha 1988a). Linear peptides with insecticidal properties, the efrapeptins, are produced by *Tolypocladium niveum*, (syn. *T. inflatum*, *B. nivea*; Gupta et al. 1991a; Krasnoff and Gupta 1991). These compounds inhibit the mitochondrial ATPase and possess antimicrobial and miticidal (acaricidal) activities. The efrapeptins differ from fungal peptaibols by their unique C-terminus which is formed by a bicyclic amine and apparently plays an important role in conferring the biological activity (Gupta et al. 1992). Of the several hundred known peptaibols none has been reported to have insecticidal activities (Berdy 2000), although apparently most of them have never been tested against insects. *T. geodes* and *T. cylindrosporum* were reported to produce “tolypin”, an insecticidal principle of unknown composition and structure (Weiser and Matha 1988b). From the zygomycete *Entomophthora virulenta* (syn. *Conidiobolus thromboides* Drechsler) two azoxybenzene-carboxylic acids (see Fig. 2) are known. The mono-acid is responsible for the insecticidal activity (Claydon and Grove 1978). Many genera within the Deuteromycotina, like *Fusarium*,