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Chemical Ecology of Fungi

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Fungi are widespread in nature and have conquered nearly every ecological niche. Fungi do not only occur in terrestrial but also in freshwater and marine environments. Moreover, fungi are known as a rich source of secondary metabolites. Despite these facts, the ecological role of many of these metabolites is still unknown and the chemical ecology of fungi has not been investigated systematically so far. This review intends to present examples for the various chemical interactions of fungi with other fungi,
10 plants, bacteria and animals and to give an overview on the current knowledge about fungal chemical ecology.

1) Introduction

2) Ecological Role of Secondary Metabolites in Fungi

2.1) Chemical Communication

15 2.2) Chemical Defence

2.2.1) Constitutive Chemical Defence

2.2.2) Wound-Activated Chemical Defence

2.2.3) Induced Chemical Defence

2.3) Symbiotic Interactions

20 2.3.1) Fungi as Endosymbionts

2.3.2) Mycorrhiza Fungi

2.3.3) Lichens

2.3.4) Symbiosis between Insects and Fungi

2.3.5) Symbiosis between Bacteria and Fungi

25 2.4) Attack and Counter-Defence

2.4.1) Mycoparasitic Fungi

2.4.2) Plant Pathogenic Fungi

2.4.3) Entomopathogenic Fungi

3) Conclusions

30 4) References



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60 1) Introduction

More than 150 years ago Charles Darwin detected that organisms adapt themselves to their environment in an evolutionary process in order to secure their survival.¹ To do so, animals but also plants, fungi and bacteria have to secure access to sufficient
65 nutrition and space and have to develop strategies to survive the attacks of competitors and predators. Different species use different strategies to be successful, for instance, there are species which reproduce very quickly and produce a large number of spores, seeds or of offspring. Thus, the survival of such a species
70 on its whole is not endangered, if a certain proportion falls victim to enemies. Another strategy is used by carnivores. They have developed a set of teeth which allow them both to attack their prey and to defend themselves actively against attacks. Other species have evolved passive means of protection by mechanical
75 barriers. For instance, some animals like the hedgehog are barbed

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and thorns are present at the surface of many plants.²

Despite the fact that plants and fungi are immobile this does not mean that these species only rely on anatomical and mechanical barriers to defend themselves, since many plants and fungi have evolved a multitude of different chemical defence strategies.³

The existence of bioactive compounds in fungi has been recognised and used by humans already in ancient times. Fruiting bodies of *Piptoporus betulinus* had been found among the belongings of the Hauslabjoch mummy, "Ötzi, the Ice Man", who had lived approximately 5300 years ago in the Alps.⁴ *P. betulinus* exhibits antimicrobial and antitumoural properties and might have already been used in the Bronze age as remedy.⁵ In ancient Chinese medicine the white rot fungus *Ganoderma lucidum* has been known as "mushroom of immortality" since more than 2000 years.⁶ Not only healing properties of fungi but also deleterious ones have been used and experienced since long times. For instance, Agrippina, the wife of the Roman emperor Claudius, probably poisoned her husband with fruiting bodies of the death cap (*Amanita phalloides*) in the year 54.⁷ Mycotoxins from fungi growing on food or food plants, such as ergot fungi of the genus *Claviceps*, caused mass poisonings in humans in the Middle Ages in Europe.⁸ The corresponding disease was called "St. Anthony's Fire".⁸ Such poisonings have even been recorded in the Assyrian and Egyptian history.⁸ Yet ergot fungi as the causative agents were not identified before the year 1764.⁸ On the other hand, ergot fungi do not only possess deleterious effects. As early as 1582 a preparation of ergot was used by midwives to evoke strong uterine contractions in pregnant women.⁸

From the early days of natural products chemistry on, chemists have been interested in the isolation and structure elucidation of bioactive secondary metabolites from fungi. The detection of the antibiotic properties of *Penicillium rubens* by Fleming⁹ in 1928 stimulated the search for new antibiotics and secondary metabolites from fungi and bacteria.¹⁰ However, research was rather focussed on the detection of compounds that might be useful as lead structures for the development of new drugs^{11–13} which might help to cure diseases than to reveal the ecological role of a secondary metabolite for a certain organism. Considerable research efforts have also been undertaken, if fungal metabolites exert deleterious effects on humans, farm animals or important crop plants. Although the first investigations on chemical ecology date back to the 19th century¹⁴ it was not before the 1960s that chemical ecology became more and important,¹⁵ since it has been recognised that a better understanding of the ecological role of secondary metabolites does not only deepen the knowledge about interactions between species but might also be useful for the development of crop protecting agents. However, chemical ecologists mainly focussed their interest on plants and insects,¹⁴ while the chemical ecology of fungi has often only been studied from a non-fungal-based perspective and has not been systematically investigated.³ This review intends to switch the perspective and to present our knowledge on the chemical ecology of fungi from a fungi-based point of view.

2) Ecological Role of Secondary Metabolites in Fungi

Fungi are widespread all over the world. So far, approximately 100000 species are known and several millions are expected to exist,¹⁶ indicating that there are probably more fungal than plant species living on earth. Obviously, fungi are organisms which are very successful in inhabiting the world.

Similarly to plants fungi produce a large number of secondary metabolites. In general, secondary metabolites are considered to be produced to warrant the producer organism an advantage.³ However, the ecological role of most fungal secondary metabolites is still unknown.³

Not only fruiting bodies of fungi but also their mycelia have to cope and interact with enemies and competitors. Short-lived fruiting bodies of fungi are often targets of fungivores and mycoparasitic fungi.^{3,17} Since fruiting bodies produce spores which are important for the sexual reproduction of fungi, many fruiting bodies of fungi contain either toxins or bitter or pungent compounds that prevent fungivores from feeding.³

Moreover, fungal mycelia have to compete with other organisms for nutrition and space.¹⁸ Since fungi are heterotrophic organisms, they depend on obtaining nutrition in form of suitable natural products, such as sugars or amino acids. To this end, fungi are either forced to decay dead organic matter or to interact with living organisms and obtain nutrition from other species. Depending on their life style three types of fungi are distinguished: Saprophytic, parasitic and symbiotic fungi.¹⁹ Saprobiotic fungi decay organic material of dead organisms.¹⁹ Parasitic fungi obtain their nutrition from living host organisms which are harmed by the parasite. Several types of parasitic fungi are distinguished in dependence of the host. For instance, mycoparasitic fungi parasitize other fungal species,²⁰ phytopathogenic fungi living plants,²¹ and entomopathogenic fungi insects.²² Symbiotic fungi also obtain their nutrition from other living organisms but they also provide the host advantages. Endosymbiotic organisms live within other living organisms, for instance endophytic fungi live within plants.²³ Mycorrhizal fungi live in symbiosis with plant roots and provide plant roots with inorganic nutrients present in the soil.²⁴ Lichens consist of an algae and a fungi which live together in symbiosis.²⁵ To interact successfully with such a multitude of other species fungi must have developed a rich chemical ecology. For instance, secondary metabolites serve for communication purposes, for chemical defence purposes,³ for symbiotic interaction purposes, for attacking other species by production of toxic compounds or for knocking out the hosts defence mechanisms.

2.1) Chemical Communication

Chemical communication is widespread in insects, which often use volatile compounds to initiate or influence a certain behaviour.²⁶ These compounds are often called infochemicals, serving as a form of language.²⁷ Chemical communication is based on chemical signals which mediate interactions between the same or different species.²⁷ Although Dick and Hutchinson recognised in 1966 that volatile compounds play a role in fungus-fungus interactions,²⁸ even today not very much is known on chemical communication of fungi with each other and other organisms, such as plants and insects.

For instance, chemical communication plays a decisive role in mating, in sporulation and in the induction of morphological changes.²⁹ In the yeast *Saccharomyces cerevisiae* the recognition of compatible sexual partners is based on pheromones in form of diffusible peptides called a-factor and α -factor.²⁹

Chemical communication between plants and fungi is also necessary for the establishment of mycorrhiza. Particularly in the last decade considerable progress has been made in the understanding of the fungal chemical signals that lead to mycorrhization of plants (see section 2.3.2).³⁰

In the chemical communication of fungi volatiles are obviously of great importance. For instance, conidiation in *Trichoderma* species is induced by (3*R*)-1-octen-3-ol (**38**), octan-3-ol and 3-octanone.³¹

In general, upon wounding (3*R*)-1-octen-3-ol is generated after activation of hydrolases and lipoxygenases from linoleic acid (see section 2.2.2).³² Thus, the concentration of (3*R*)-1-octen-3-ol is dramatically increased in injured fungal tissues.

Both the mycelia and the fruiting bodies of many fungi produce (3*R*)-1-octen-3-ol which has been reported to induce plant defence in lower concentrations³³ and to exhibit toxic effects and induce an oxidative burst on plants at higher concentrations.³⁴

Moreover (3*R*)-1-octen-3-ol acts as fungistatic and fungicidal agent³⁵ and attracts certain insects, such as certain wood-living beetles³⁶ and the phorid fly *Megasella halterata*³⁷ which feed on fruiting bodies and might contribute to the distribution of fungal spores.

Truffles emit volatiles that attract insects or mammals which spread the spores of the fruiting bodies.³⁸ So far, more than 200 volatiles have been reported from different tuber species³⁹ but the ecological role of most volatiles is still unknown.³⁴ Dimethyl disulfide is present in many truffles including the famous Périgord black truffle (*Tuber melanosporum*).⁴⁰ It is suspected to be one of the truffles attractants for mammals, such as pigs, while pigs are not attracted by the steroidal pheromone 5 α -androstrenol which is also a constituent of *T. melanosporum*.³⁸

Dimethyl disulfide and dimethyl trisulfide are also constituents of ripe fruiting bodies of the stinkhorn (*Phallus impudicus*).⁴¹ Both dimethyl disulfide and dimethyl trisulfide are suspected to attract flies of the genera *Calliphora*, *Lucilia* and *Sarcophaga*.⁴¹ In accordance with this finding the content of dimethyl trisulfide is considerably higher in ripe fruiting bodies than in egg-shaped ones.⁴²

In *Penicillium decumbens* (+)-thujopsene has been identified as volatile which exhibits autoregulatory properties of the growth of *P. decumbens*.⁴³ Moreover, thujopsene negatively affected the mycelial growth of other fungi, such as *Aspergillus sydowii*.⁴³

2.2) Chemical Defence

Despite the fact that the ecological role of many fungal secondary metabolites is still unknown, there are already a number of investigations which show that chemical defence is not only widespread in plants but also in fungi.³ Chemical defence compounds are usually effective against animals, plants or other fungi, thus exhibiting toxic, pungent, bitter, herbicidal or fungicidal properties.

To date at least three fundamentally different chemical defence mechanisms are known.³ While constitutive chemical defence

relies on permanently present bioactive secondary metabolites, wound-activated chemical defence is based on the conversion of an inactive precursor into a bioactive defence compound that is only generated upon injury. In induced chemical defence compounds are synthesised *de novo* on demand.

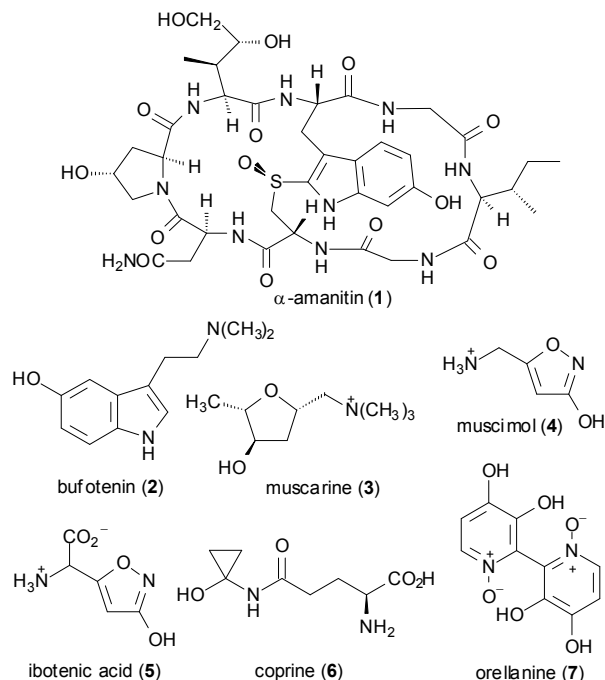
2.2.1) Constitutive Chemical Defence

The identification of a certain secondary metabolite as constitutive chemical defence compound requires to perform a bioassay-guided screening of the corresponding compound against potential enemies or competitors.³

2.2.1.1) Toxins

The deadly poisonous properties of the death cap (*Amanita phalloides*) have already been known in ancient times.⁷ The toxicity of the fruiting bodies of this species is caused by cyclic octapeptides, such as α -amanitin (**1**),^{44,45} which allosterically inhibits the human RNA polymerase II.⁴⁶

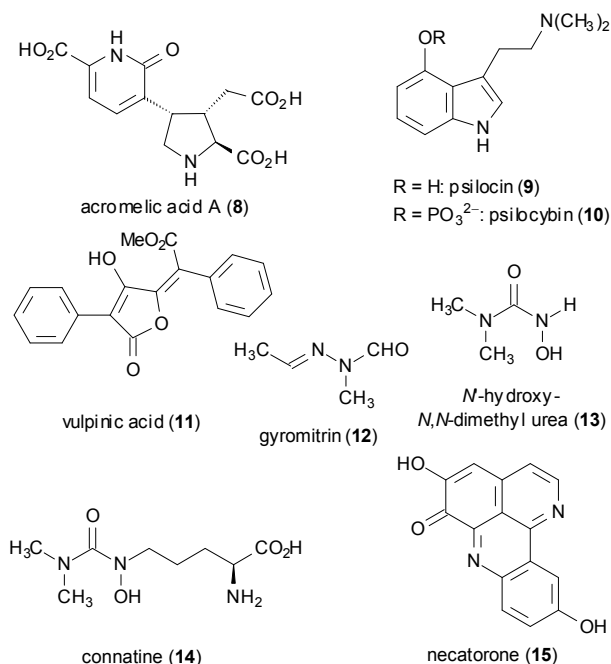
Amanita citrina which is closely related to the death cap contains the toxin bufotenin (**2**).⁴⁷ The fly agaric (*Amanita muscaria*, French: amanite tue-mouches, German: Fliegenpilz) is a well-known hallucinogenic mushroom.^{48,49} Its name points to its insecticidal properties. Even in medieval ages it was known, that milk mixed with pieces of the fly agaric can be used to kill flies which are dazed and drown in the milk.⁵⁰ The toxic constituents are muscarine (**3**), muscimol (**4**) and ibotenic acid (**5**).^{48,49} Ibotenic acid interacts with the glutamic acid receptor and muscimol is able to bind to the GABA receptor, thus both compounds are acting as neurotoxins causing dizziness and confusion.^{48,49}



Coprine (**6**) is the toxic constituent of the common ink cap (*Coprinus atramentarius* = *Coprinopsis atramentaria*).⁵¹ It is also present in some other *Coprinus* species. The coprinus syndrome, nausea, vomiting and facial reddening, only occurs if the fruiting bodies are ingested together with alcohol, since coprine (**6**) is

degraded upon ingestion to glutamic acid and the biologically active substance 1-aminocyclopropanol.⁵² This compound inhibits the enzyme alcohol dehydrogenase which is essential to detoxify the intermediate acetaldehyde in the oxidative detoxification process of ethanol to acetic acid.⁵² While humans usually recover completely from the coprinus syndrome, ingestion of *Cortinarius orellanus* and *Cortinarius rubellus* can be lethal. The nephrotoxicity of *C. orellanus* was not recognised before the 1950s when a mass intoxication led to several cases of death in Poland.⁵³ The causative agent orellanine (7) was structurally elucidated in 1979.⁵⁴ The fruiting bodies itself contain orellanine (7) in form of its 4,4'-diglucoside which easily degrades to orellanine if the work-up procedure is not appropriate.⁵⁵

Clitocybe acromelalga contains the toxin acromelic acid (8) leading to long-lasting extreme pain and erythema.⁵⁶ Other toxins present in fruiting bodies of mushrooms are the hallucinogenic secondary metabolites psilocin (9) and psilocybin (10) in various *Psilocybe* species.^{57,58} The toxin vulpinic acid (11) occurs in *Pulveroboletus ravenelii* and in the lichen *Letaria vulpina*.⁵⁹ The latter was used to kill wolves and foxes. Gyromitrin (12) is an other fungal toxin present in *Gyromitra esculenta*.⁶⁰ It leads to nausea, diarrhea and dizziness. Even nowadays fruiting bodies of mushrooms which have been estimated to be edible turn out to be unhealthy or even poisonous. The white dome-cap (*Lyophyllum connatum*) was considered to be a good edible mushroom until it turned out that it contains mutagenic *N*-hydroxy-*N,N*-dimethyl urea (13) and the amino acid connatine (14).⁶¹ In *Lactarius necator* mutagenic necatorone (15) is present.⁶² In 2001 two casualties were reported after ingestion of *Tricholoma equestre*,⁶³ a delicious tasting mushroom species. The responsible toxin is still unknown. So far, studies on the ecological role of toxins from fruiting bodies of fungi are rare. However, an investigation with the fungivorous opossum demonstrates that at least this animal learns to avoid toxic fungi, such as *A. muscaria*.⁶⁴⁻⁶⁶



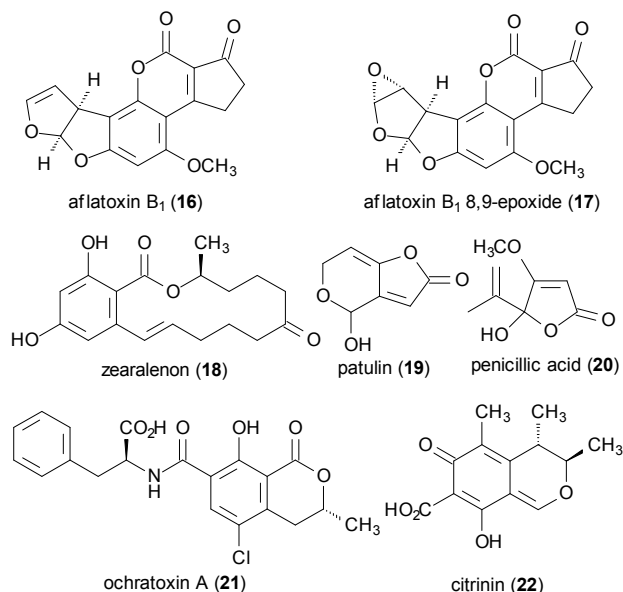
Toxic compounds are not only present in fruiting bodies of fungi but also occur in moulds growing on plants and on decaying fruits. Toxins present in moulds are referred to as mycotoxins.⁶⁷

The ecological role of many mycotoxins is likely to keep away unwanted competitors from decaying organic matter that serves moulds as nutrition.⁶⁸ Consequently, mycotoxins are often toxic to insects and other fungi. However, in many cases the primary ecological role of mycotoxins is not well investigated since mycotoxin research was so far mostly focussed on their deleterious effects on humans and animals which serve as food source for humans.⁶⁶

While the toxic properties of ergot fungi, such as *Claviceps purpurea*, growing on rye plants, producing ergot alkaloids (see section 3.2.1) causing the so-called St. Anthony's fire have been known for centuries,⁸ the deleterious effects of other moulds have long been overlooked.

In 1960 a mass intoxication of turkeys in Great Britain led to the death of the whole animal stock. Intensive investigations revealed that the turkeys food contained groundnuts which were contaminated with the mould *Aspergillus flavus* which produces hepatotoxic and cancerogenic aflatoxins.⁶⁹ Of all known aflatoxins aflatoxin B₁ (16) is considered to be the most toxic to humans.⁶⁹ The toxicity of aflatoxin B₁ (16) is attributed to its potential to induce oxidative stress. In the liver it is converted to the reactive epoxide 17 which binds to DNA and proteins leading to tumourigenesis.⁶⁹ *A. flavus* might use aflatoxin B₁ to protect its substrate from feeding insects since aflatoxin B₁ exhibits insecticidal activity towards *Drosophila melanogaster*.⁷⁰

Zearalenone (18) is a mycotoxin that is produced by *Fusarium* species, such as *Fusarium graminearum*, growing on cereal crops.⁷¹ It has relatively low acute toxicity but causes hyperestrogenism in farm animals and humans due to its structural similarity to estradiol.⁷¹ The ecological role of zearalenone is not well investigated but it is known that it exhibits antifungal activity,⁷² thus probably helping the fungus to keep competing fungi away from its food source.



The mycotoxin patulin (19) is produced by *Penicillium* and

Aspergillus species, for instance by *Penicillium expansum*. These moulds decompose ripe fruits, such as apples.⁷³ Since patulin is immunotoxic, teratogen and carcinogen to humans,⁷⁴ juices have to be strictly monitored for contamination with patulin. Patulin

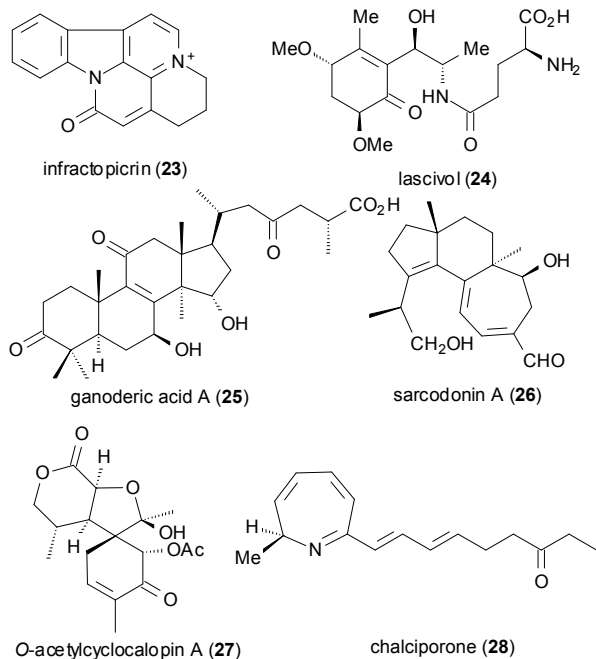
(19) exhibits insecticidal activity towards *D. melanogaster*,⁷⁵ thus preventing at least to some degree insects from feeding on the food source of *P. expansum*. Penicillic acid (20) is biosynthetically related to patulin. Penicillic acid is widespread in *Penicillium* and *Aspergillus*

species and acts as a mutagenic and carcinogenic toxin.⁶⁷ Penicillic acid exhibits antifungal, antibacterial and herbicidal activity.⁷⁶ Obviously, penicillic acid helps to prevent competitors from growing near fungi which contain this toxin. Ochratoxin A (21) and citrinin (22) are nephrotoxins.^{67,77} Ochratoxin A is produced by *Aspergillus ochraeus*, *Penicillium viridicatum* and some other fungal species and is able to contaminate foodstuffs, for instance grains.⁶⁷ Citrinin occurs in *Aspergillus*, *Monascus* and *Penicillium* species and contaminates grains.⁶⁷ Ochratoxin A and citrinin interfere with the microbial iron uptake.⁷⁸ Moreover, ochratoxin A and citrinin exhibit insecticidal activity against *Drosophila* species.⁷⁹ Competing insects might be prevented by these means from feeding on 21 and 22 producing moulds and microbes from growing in the vicinity of these moulds.

Several other fungal secondary metabolites exert adverse effects on humans. For instance, this applies to the trichothecenes which cause alimentary toxic aleukia, if contaminated cereals are consumed.⁸⁰ However, these fungal toxins will be discussed in section 2.4.2, since they are in the first line plant pathogens which harm their host plants.

2.2.1.2) Pungent and Bitter Compounds

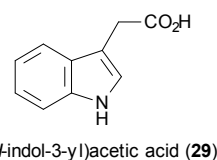
Bitter and pungent compounds taste not only unpleasant to humans, but also to other mammals, such as the opossum.⁶⁴⁻⁶⁶ Therefore, it is not astonishing that many fruiting bodies of fungi contain bitter and pungent compounds.



While the bitter taste of *Cortinarius infractus* is caused by the alkaloid infractopicrin (23),⁸¹ the bitter taste of *Tricholoma lascivum* is attributed to the cyclohexenone derivative lasciviol (24).⁸² *Ganoderma lucidum* contains bitter triterpenes, such as ganoderic acid A (25).⁸³ Several diterpenes, for instance sarcodonin A (26), are responsible for the bitter taste of *Sarcodon scabrosus*.⁸⁴ In *Boletus calopus* and *Boletus radicans* bitter sesquiterpenes, for instance *O*-acetylcycloalopine A (27), are present.⁸⁵ The peppery bolete (*Chalciporus piperatus*; German: Pfefferröhrling) exhibits a characteristic pungent taste due to the presence of the 2*H*-azepine alkaloid chalciporone (28).^{86,87} Also many *Lactarius* and *Russula* species taste pungent within a few seconds after injury, since pungent compounds, such as velleral, are generated on injury of the fruiting bodies (see chapter 2.2.2).⁸⁸ Apart from these examples, the structures of the bitter or pungent compounds of some prominent species including the fruiting bodies of *Tylopilus felleus* are still unknown. This mushroom is often confused with the deliciously tasting *Boletus edulis* making mushroom dishes contaminated with *T. felleus* inedible.

2.2.1.3) Plant Pathogens

In general, mycelia of fungi are also able to exert herbicidal activity against plant growth in order to keep unwanted competitors away. For instance, around the black truffle (*T. melanosporum*), a "burnt" zone is observed where the plant cover is scarce.⁸⁹ It is known that the mycelium of this species releases both ethylene and 3-indole acetic acid (29) which act as herbicides above certain concentrations.^{90,91} Also (*R*)-1-octen-3-ol (38) which is released by many fungal species on injury exerts toxic effects on plants at higher concentrations.³⁴ In contrast to the scarce knowledge on herbicidal effects in the chemical defence of non-parasitic fungi, much more is known about herbicidal compounds from plant pathogenic fungi (see chapter 2.4.2).



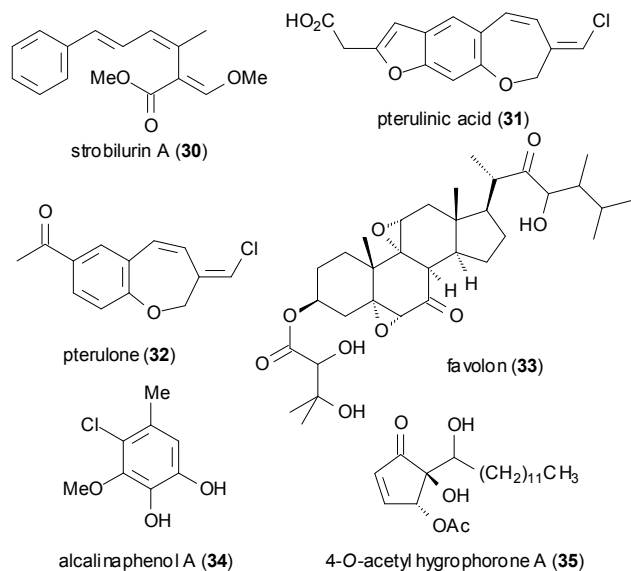
2.2.1.4) Fungicides

Fungal mycelia have to compete with other fungi for nutrition and space. Moreover, fungal mycelia and fruiting bodies of fungi are potential victims of mycoparasitic fungi which parasitise other species. Therefore, several fungi contain fungicides which protect mycelia and fruiting bodies from mycoparasites and competing fungi. The pinecone cap (*Strobilurus tenacellus*) is the most prominent example of a fungus producing fungicides.⁹² *S. tenacellus* is a saprophytic fungus which develops small fruiting bodies which are growing on pine cones. In the 1970s the fungicidal principle of this species was identified from mycelial cultures to be a previously unknown secondary metabolite which was named strobilurine A (30).^{93,94} Till now, many more representatives of this class of antifungal compounds have been detected also in several other fungal species. *S. tenacellus* is capable to prevent growth of other fungi on pine cones which are

inhabited by *S. tenacellus* due to the presence of strobilurine A (30).⁹⁵ The antifungal activity of the strobilurines is based on binding reversibly to the ubihydroquinone oxidation centre of the cytochrome bc₁ complex, thus inhibiting electron transfer in the fungal respiratory chain. *S. tenacellus* itself is resistant to its own fungicide since its bc₁ complex is point-mutated.⁹⁶ Strobilurines turned out to be new lead structures addressing a new target in fungi with their β-methoxy acrylate pharmacophore. Therefore, the strobilurines have been developed into commercially available fungicides, such as kresoxim-methyl and azoxystrobin, which play an important role in crop protection.⁹⁷

Fungicidal secondary metabolites have also been identified in other mycelial cultures and fruiting bodies. For instance, the fungicides pterulinic acid (31) and pterulone (32) have been isolated from mycelial cultures of the *Pterula* species 82168^{98,99} and favolon (33) from cultures of the *Favolaschia* species 87129.^{100,101} Mycelial cultures of *Mycena alcalina* produce antifungal phenolic compounds such as alcalinaphenol A (34).¹⁰² Hygrophorones, such as 4-*O*-acetyl hygrophorone (35), are fungicides present in different *Hygrophorus* species.¹⁰³ Fungicidal compounds appear to be relatively widespread in fungi. Particularly saprophytic fungi, such as *S. tenacellus*, secure their habitat by these means for themselves and exclude undesired competitors from growing in their surrounding.

Fungicidal compounds are also produced by moulds, for instance by *Trichoderma harzianum*.¹⁰⁴ This species is a mycoparasitic fungus which shows antagonism against a broad spectrum of other fungi and contains antifungal metabolites, such as 6-pentyl-α-pyrone (99), harzianolide (100) and harzianopyridone (101) (see chapter 2.4.1).¹⁰⁴



2.2.2) Wound-Activated Chemical Defence

In wound-activated chemical defence the defence compound is only generated upon wounding usually after activation of enzymes which convert inactive precursor molecules into the corresponding defence compounds.³ Typically, the conversion of precursors into active defence compounds requires only a few

seconds.^{88, 105}

So far, only some wound-activated chemical defence mechanisms are known from fungi. The reason for this is that the presence of wound-activated chemical defence mechanisms has often been overlooked since most fungi were only investigated for the presence of bioactive compounds.³ During the work-up procedure of fungal material in many cases no care was taken about possible activation of enzymes which might degrade constituents originally present in intact fungi. Moreover, inactive precursors cannot be detected directly in a test for bioactivity. Therefore, to identify wound-activated chemical defence mechanisms in fungi, it is necessary to search systematically for the presence of such defence mechanisms.

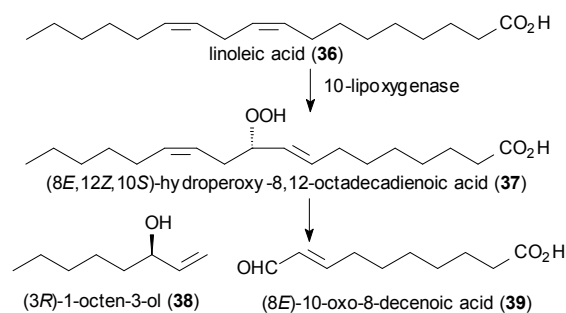
In general, two methods are suitable to detect wound-activated chemical defence mechanisms. The first method is based on comparison of the bioactivity of extracts between intact and injured fungi.¹⁷ By this method fruiting bodies of a considerable number of fungi have already been investigated for antibiotic, antifungal, nematocidal and insecticidal activity.¹⁷ Despite the fact that several species show an increased biological activity on injury, this method has the disadvantage, that defence compounds and the corresponding precursor cannot be easily identified.

The second method to detect wound-activated chemical defence mechanisms rests upon a comparison of the metabolite patterns of intact and injured fungi.^{3,106} For instance, this can be done by HPLC-UV, LC-MS or GC-MS based comparative metabolite profiling of extracts from intact and injured fungi.¹⁰⁶ Compounds which only occur upon injury are those which might play a role in wound-activated chemical defence. Compounds which are present in intact fruiting bodies but not or to a lesser extent in injured ones might be the corresponding inactive precursors.³ To confirm the presence of a wound-activated chemical defence mechanism it is also necessary to demonstrate that compounds which are only present on injury exhibit bioactivity against relevant predators, parasites of competitors of the fungal species investigated.³

Although changes of taste, odour and colour have been known to occur after injury of fruiting bodies of mushrooms already for centuries, the potential ecological role of these compounds has not been recognised for a long time. So far, most wound-activated chemical defence mechanisms known from fungi are based on the activation of inactive precursors by hydrolysis, oxidation or lipid peroxidation to the corresponding defence compounds.³

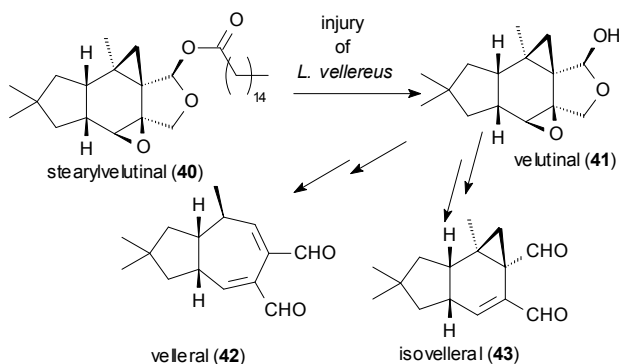
A very widespread response to wounding occurring in plants, animals and fungi is the activation of hydrolases and lipoygenases leading to the liberation of free fatty acids and subsequent oxidation of linoleic acid (36) to hydroperoxides.¹⁰⁷

In fungi, upon injury, linoleic acid is oxidised and degraded via the intermediate (8*E*,12*Z*,10*S*)-10-hydroperoxy-8,12-octadecadienoic acid (37) to (3*R*)-1-octen-3-ol (38) and (8*E*)-10-oxodec-8-enoic acid (39).^{32,108} (8*E*)-10-oxodec-8-enoic acid (39) has been found in increased amounts in wounded fruiting bodies,^{109–111} for instance in *Marasmius oreades*, and seems to stimulate mycelial growth and stipe elongation in *Agaricus bisporus*.¹¹² Both (3*R*)-1-octen-3-ol (38) and (8*E*)-10-oxodec-8-enoic acid (39) exhibit antifungal activities. For instance these compounds inhibit the growth of *Penicillium expansum*.¹¹³ Consequently, they might play a role in the wound-activated chemical defence of fungi.



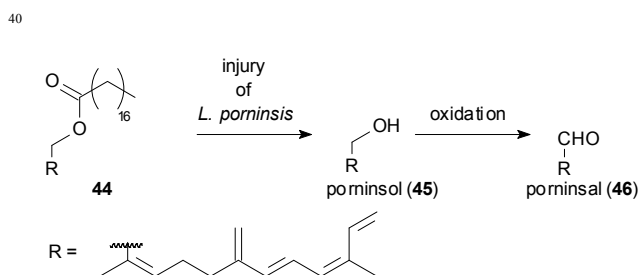
Scheme 1. Wound-activated generation of (3R)-1-octen-3-ol (38).

While the chemical defence with (3R)-1-octen-3-ol (38) is present in most if not all fungi,^{114–117} most other wound-activated chemical defence mechanisms known so far are restricted to one or a few species. For instance, only *Lactarius* and *Russula* species seem to use the pungent tasting compounds velleral (42) and isovelleral (43) as defence compounds.^{118,119} These secondary metabolites have already been isolated from *Lactarius* species forty years ago but it was not before the 1980s that these compounds have been identified as extraction artefacts.⁸⁸ A TLC comparison of extracts from intact and artificially injured fruiting bodies revealed the presence of stearylvelutinal (40) as precursor of the degradation products velutinal (41), velleral (42) and isovelleral (43) in intact fruiting bodies, while injured fruiting bodies only contained the pungent tasting degradation products.⁸⁸ The pungent tasting compounds velleral (42) and isovelleral (43) are strong antifeedants. For instance, the opossum species *Didelphis virginiana* avoids isovelleral-producing fungi.^{64–66} Moreover, isovelleral acts as an insecticide against the confused flour beetle (*Tribolium confusum*).¹²⁰

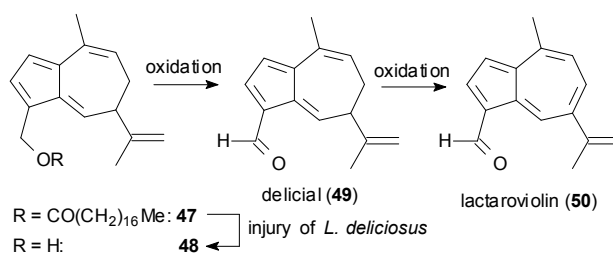
Scheme 2. Generation of velleral (42) in *Lactarius* species.

α,β -Unsaturated aldehydes, such as 42 and 43, are able to react with nucleophiles, for instance with the ϵ -amino group of lysine residues in proteins. Moreover, the reaction of 1,4-dialdehydes with amine residues in proteins has been associated with their pungent taste.^{121–123} Bioactive 1,4-dialdehydes are not only generated in the wound-activated chemical defence of fungi, since analogous examples have been reported from plants,^{124–125} algae¹²⁶ and animals.^{127–130} Another wound-activated chemical defence mechanism is known from *Lactarius pomninsis* which contains farnesane esters, such as

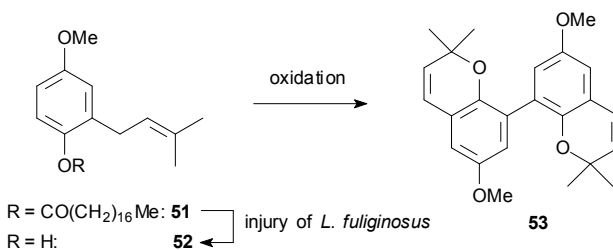
44.¹³¹ Upon injury of the fruiting bodies, these mild tasting esters are hydrolysed to pomnisol (45) and subsequently oxidised to the bitter tasting reactive aldehyde pomninal (46).¹³¹

Scheme 3. Wound-activated generation of pomninal (46) in *L. pomninsis*.

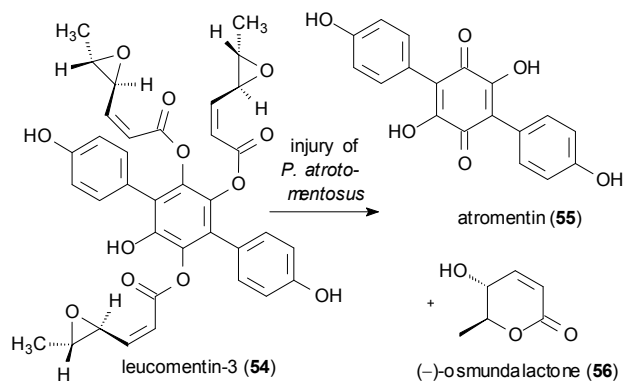
Intact fruiting bodies of *Lactarius deliciosus* and *Lactarius deterrimus* contain the guaiane ester 47.¹³² Upon injury 47 is hydrolysed to the corresponding free alcohol 48 which is then oxidised to the aldehydes delicial (49) and lactaroviolin (50).¹³² However, so far investigations are missing, proving delicial (49) or lactaroviolin (50) to be defence compounds, since *L. deliciosus* and *L. deterrimus* are edible mild tasting species.

Scheme 4. Wound-activated of delicial (49) in *L. deliciosus*.

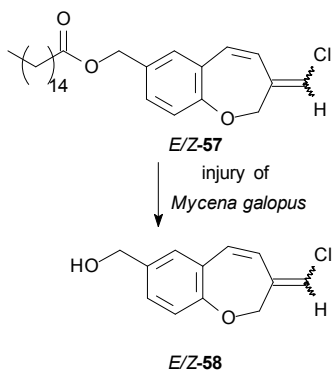
The wound-activated chemical defence of fruiting bodies of *Lactarius picinus* and *Lactarius fuliginosus* is based on the tasteless phenol ester 51 which is present in intact fruiting bodies. In injured fruiting bodies the ester 51 is hydrolysed to the acrid tasting fungicidal free phenol 52 which is slowly oxidised to a mixture of benzofuran and chromene pigments, such as 53.¹³³

Scheme 5. Wound-activated chemical defence in *L. picinus*.

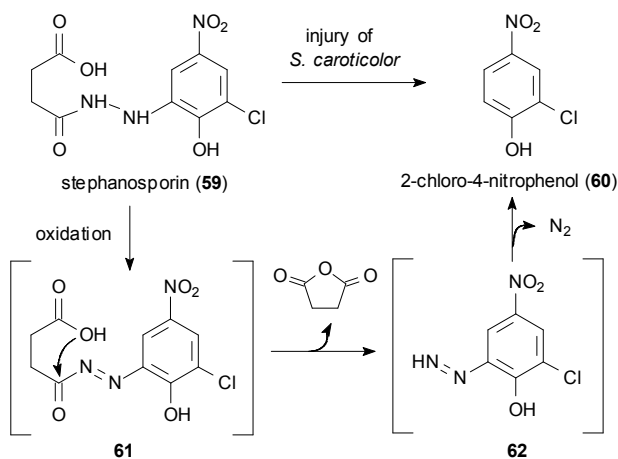
Intact fruiting bodies of *Paxillus atrotomentosus* contain leucomentins, for instance leucomentin-3 (54).^{134–136} Upon injury of the fruiting bodies, these inactive precursors are hydrolysed and converted to atromentin (55) and (+)-osmundalactone (56).^{134–136} (–)-Osmundalactone is a feeding deterrent which occurs in the fern *Osmunda japonica*.¹³⁷

Scheme 6. Wound-activated chemical defence in *P. atrotomentosus*.

The milking bonnet (*Mycena galopus*) releases a white latex if the fruiting bodies are cut or bruised.¹⁰⁶ Intact fruiting bodies contain benzoxepine esters, for instance **57**. Upon injury, the inactive esters are hydrolysed to the corresponding free alcohols, such as **58**, which exhibit antifungal activity.¹⁰⁶ By this means, the tiny fruiting bodies of *M. galopus* might protect themselves from other fungi.

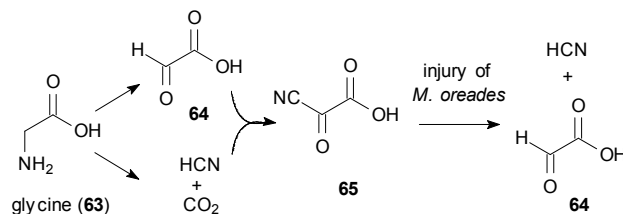
Scheme 7. Wound-activated chemical defence in *M. galopus*.

The carrot truffle (*Stephanospora caroticolor*), a gasteromycete uses a very special wound-activated chemical defence mechanism.¹³⁸

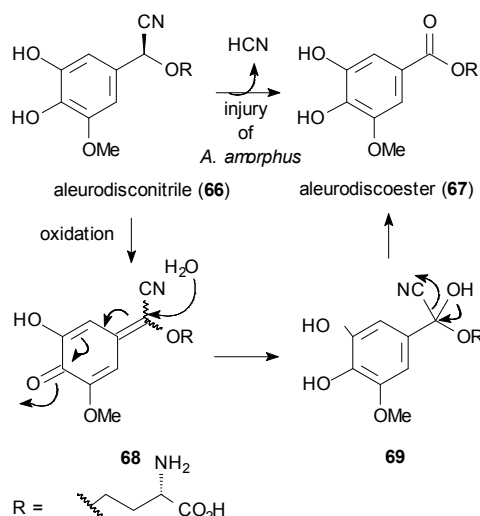
Scheme 8. Wound-activated chemical defence in *S. caroticolor*.

In intact fruiting bodies the inactive precursor stephanosporin (**59**) is present. In injured fruiting bodies stephanosporin is oxidised to the corresponding diazene **61** which decomposes to 2-chloro-6-diazenyl-4-nitrophenol (**62**) and succinic acid anhydride. Then, the phenol **62** decomposes to nitrogen and the fungicide 2-chloro-4-nitrophenol (**60**).¹³⁸

Many fungi are cyanogenic. A recent investigation on the production of hydrocyanic acid in fruiting bodies and mycelia of *Marasmius oreades* revealed that the free cyanohydrin **65** decomposes on injury to HCN and glyoxylic acid (**64**).¹³⁹ The cyanohydrin **65** is biosynthetically derived from glycine (**63**).¹³⁹ Since several other cyanogenic mushrooms also contained the cyanohydrin **65**, this defence mechanism appears to be widespread in fungi.¹³⁹

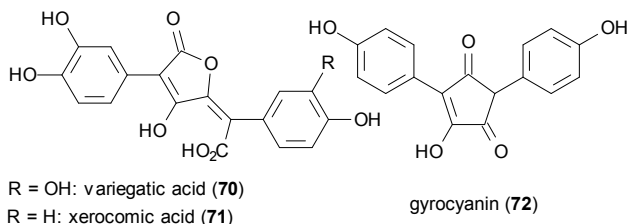
Scheme 9. Biosynthesis and wound-activated generation of HCN in *M. oreades*.

Other wound-activated chemical defence mechanisms with hydrocyanic acid are known from plants,¹⁴⁰ animals¹⁴⁰ and bacteria¹⁴¹ but also from the crust fungus *Aleurodiscus amorphus*.¹⁰⁵ Fruiting bodies of this species contain the tailor-made inactive precursor aleurodisconitrile (**66**) which is oxidatively converted upon injury via **68** and **69** to hydrocyanic acid and aleurodiscoester (**67**).¹⁰⁵

Scheme 10. Wound-activated generation of HCN in *A. amorphus*.

Many more examples are known in which injury of fungal fruiting bodies has been linked to a chemical reaction of fungal constituents. For instance, the oxidation of variegatic acid (**70**),¹⁴²

xerocomic acid (71)¹⁴³ or gyrocyanin (72)^{144,145} to quinone methide anions is responsible for the blueing of many boletes upon injury.^{146,147} However, the ecological significance of these and many other reactions is still not well-investigated.

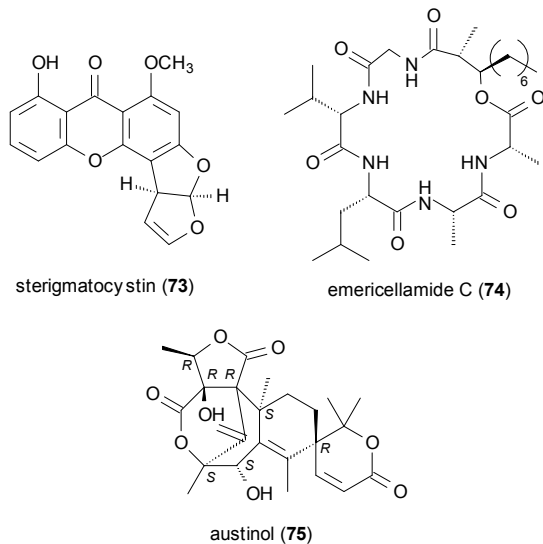


2.2.3) Induced Chemical Defence

Induced chemical defence is based on the *de novo* synthesis or a significant increase of a defence compound after expression of the corresponding biosynthesis genes.³ Consequently, the production of a defence compound by induced chemical defence takes much more time than in wound-activated chemical defence and often requires several hours. While it is a disadvantage that the reaction to a threat is considerably delayed in induced chemical defence, the major advantage of this defence strategy is that it is saving resources, since defence compounds are only synthesised in significant amounts when needed.

An induced chemical defence mechanism can be identified by recording metabolite profiles in a time-dependent manner after injury. Moreover, compounds which are slowly upregulated after wounding have to be examined for their bioactivity against relevant enemies.

While there are many examples for induced chemical defence in plants,¹⁴⁸ our knowledge on induced chemical defence in fungi is scarce,¹⁴⁹ probably due to the following reasons: Fruiting bodies of mushrooms are usually short-lived entities, which often cannot be cultivated. Consequently, it is difficult to investigate fruiting bodies of fungi for the presence of induced chemical defence. Moreover, a slow reaction to threats by induced chemical defence might not be very suitable for short-lived fruiting bodies.



So far, no example for induced chemical defence in fungal fruiting bodies is known. However, it can be expected that induced chemical defence is common in fungal mycelia. An investigation on induced defence shows that the production of fungicidal strobilurines is upregulated in mycelia of *S. tenacellus* if mycelia of this species is co-cultivated together with other competing fungi.¹⁵⁰

Recently, it has been demonstrated that grazing of the springtail species *Folsomia candida* on the filamentous fungus *Aspergillus nidulans* leads to an enhanced production of the mycotoxin sterigmatocystin (73) and other bioactive secondary metabolites, such as emericellamide C (74) and austinol (75).¹⁵¹ Similarly, *A. nidulans* reacts to feeding of *Drosophila melanogaster* by upregulation of genes of the sterigmatocystin biosynthesis.¹⁵²

2.3) Symbiotic Interactions

Fungi have evolved a variety of symbiotic relationships to plants, for instance, endosymbiotic fungi grow within plants,¹⁵³ mycorrhizal fungi interact symbiotically with plant roots²⁴ and in lichens fungi interact with algae.²⁵ Moreover, symbiotic relationships between fungi and insects and between fungi and bacteria are known.

2.3.1) Fungi as Endosymbionts

Endophytic fungi live in a mutualistic relationship within plant tissues without exerting negative effects to the plant.¹⁵³ Endophytic fungi and bacteria are present in nearly every plant¹⁵⁴ with endophytic fungi are occurring more frequently than endophytic bacteria.¹⁵⁵

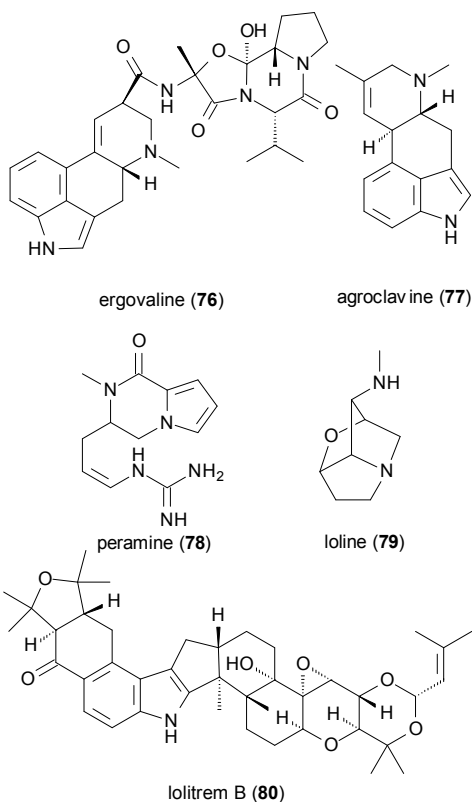
Although endophytic fungi have already been discovered in seeds of the grass *Lolium temulentum* in 1898,¹⁵⁶ the chemical ecology of endophytes largely remained unexplored until the 1970s.¹⁵⁷ However, at the onset of the year 1942 the new grass species tall fescue (*Festuca arundinacea*) originating from Europe was introduced in the USA under the name Kentucky 31 in agriculture due to its superior growing properties.¹⁵⁸ At the same time many framers using the new grass species noticed health problems among their cattle which were strikingly similar to ergotism.¹⁵⁷ However, the grass was not infected with *Claviceps* species known to cause ergotism.¹⁵⁷ It took several decades to identify the culprit as the endophyte *Neotyphodium coenophialum*. The latter produces ergopeptide alkaloids, such as ergovaline (76) which are highly toxic to feeding mammals and insects,¹⁵⁹ thus protecting *F. arundinacea* from overgrazing.¹⁵⁷

The recognition that endophytic fungi are able to produce potent bioactive compounds which exhibit protective effects to plants boosted research for new secondary metabolites from endophytic fungi. Nowadays, at least several hundred secondary metabolites from endophytic fungi are known, including all important classes of secondary metabolites, such as alkaloids, terpenoids and polyketides.^{160,161}

Endophytic fungi are usually isolated after taxonomic determination of the endophyte-containing plant material. For the isolation of an endophyte, the plant material is cut into small pieces which are surface-sterilised, for instance with 70% ethanol.¹⁶¹ The plant segments are transferred to agar plates and incubated at room temperature. Endophytic fungi often grow slowly on the plant pieces after an incubation time of several

weeks. To eliminate bacterial contaminations the endophytic fungi are usually transferred to new plates which are supplemented with antibiotics, such as ampicillin and streptomycin. The species identification is usually based on the microscopic examination of the host tissue, on the morphological characterisation of the spores and on an 18S rDNA and 5.8S rDNA sequence characterisation.¹⁶¹

So far, the ecological roles of most secondary metabolites from endophytic fungi are unknown. Nevertheless, there are already several cases in which the chemical ecology of endophytic fungi is well-investigated. Some of them are presented below.



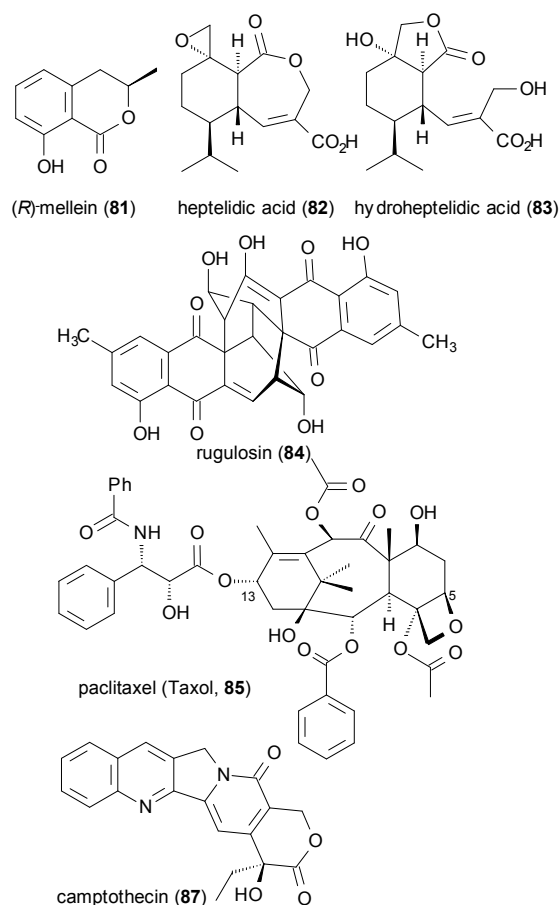
In tall fescue, ryegrass and many other grasses endophytes of the genus *Neotyphodium* are present. These species contain – as already mentioned – ergot alkaloids, such as ergovaline (76), which is obviously the causative agent for the toxicosis of cattle consuming infected tall fescue.¹⁵⁷ Moreover, ergot alkaloids are neurotoxic to insects.¹⁶² Ergoline alkaloids are also present in morning glory species such as *Ipomoea asarifolia*.¹⁶³ The plants themselves do not contain genes necessary for the biosynthesis of ergoline alkaloids. Instead, the plants harbour endophytic fungi that are equipped with the genes necessary for the biosynthesis of ergoline alkaloids. Interestingly, ergoline alkaloids have been found nearly exclusively in the plants but not in the associated epibiotic fungi, indicating the presence of a transport system for the translocation of the alkaloids.¹⁶³ Besides ergot alkaloids *Neotyphodium* species produce the indole alkaloid agroclavine (77) which is toxic to some insects and mammals¹⁶⁴ and the pyrrolopyrazine alkaloid peramine (78)¹⁶³ which is toxic to insects but not to mammals.¹⁶³ Endophyte-infected grasses, for instance *Festuca arundinacea* infected with *N. coenophialum*, contain aminopyrrolizidine alkaloids, such as loline (79), which

are highly effective insecticides.^{165,166} Furthermore, grass endophytes, for instance *Epichloe festucae* and *Neotyphodium lolii*, produce tremorgenic indole terpenes, such as lolitrem B (80).¹⁶⁷ The tall fescue endophyte *Acremonium coenophialum* is also capable of producing the plant growth-promoting hormone indole-3-acetic acid (IAA, 29) which might cause strong plant growth in infected tall fescue.¹⁶⁸ Consequently, fungal endophytes of grasses are able to protect their hosts against predators and to provide them an advantage against competitors thus often making endophyte-infected grasses the dominant species.

Endophytes are not only effective protectants in grasses but also in several other plant species. The twigs of *Forsythia viridissima* host an endosymbiotic *Pezizula* species that produces the strongly fungicidal and herbicidal isocoumarin mellein (81).¹⁶⁹

The balsam fir (*Abies balsamea*) hosts an endophytic *Phyllosticta* species which produces the terpenes heptelic acid (82) and hydroheptelic acid (83).¹⁷⁰ These compounds are toxic to larvae of the spruce bud worm (*Choristoneura fumiferana*).¹⁷⁰ Moreover, the fungus *Hormonema dematioides* present as endophyte in the balsam fir produces the insecticidal quinone rugulosin (84).¹⁷⁰

The potent anticancer agent paclitaxel (Taxol, 85) originating from the bark of the Pacific yew (*Taxus brevifolia*) is used to treat ovary cancer.^{171,172} The Pacific yew contains the endophytic fungus *Taxomyces andreanae* which has been shown by Stierle and Strobel to produce paclitaxel in *in vitro* culture.¹⁷³



However, the production of **85** is obviously extremely low. For instance, Kayser *et al.* succeeded in detecting the taxol biosynthesis key gene taxadiene synthase in *T. andreanae* but were not able to confirm the presence of **85** in cultures of *T. andreanae*.¹⁷⁴ The ecological role of taxol might consist in protecting the trees from infection by parasitic fungi since paclitaxel (**85**) exhibits strong activity against fungi, such as the plant-pathogenic oomycete *Phytophthora capsici*.¹⁷⁵ The plants *Nothapodytes nimmoniana* and *Camptotheca acuminata* produce the strong antineoplastic agent camptothecin (**86**).¹⁷⁶ Derivatives of camptothecin (**86**) are used to treat malign tumours. The ecological role of camptothecin in the plants is to protect them from insects, since it exhibits strong insecticidal properties. Recently, the endophytic fungus *Fusarium solani* was isolated from the bark of *C. acuminata* and shown to produce camptothecin (**86**).¹⁷⁷ However, the fungus requires the enzyme strictosidine synthase from the plant to be able to synthesise camptothecin.¹⁷⁸ Moreover, *ex planta* subculturing of the endophyte lead to a decreasing production of camptothecin (**86**) due to the instability of the fungal camptothecin biosynthesis genes when cultured *ex planta*. These observations show that the various interactions between plants and endosymbiotic fungi are not-well understood at present. Obviously, there are still many obstacles to overcome before cultures of endophytic fungi can be used for the production of bioactive compounds.¹⁷⁹

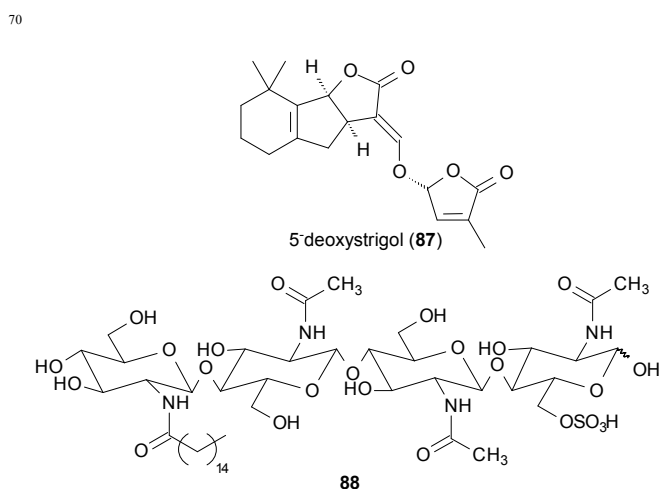
2.3.2) Mycorrhiza Fungi

The symbiotic relationship between the roots of a vascular plant and a fungus has already been recognised in 1885 and named mycorrhiza.¹⁸⁰ Two types of mycorrhiza are known, namely the endomycorrhiza and the ectomycorrhiza.²⁴ An endomycorrhiza is present, if the cortical cells of the plant root are penetrated by the fungus, while ectomycorrhizal fungi¹⁸¹ are only extracellularly attached to plant roots. Mycorrhization occurs in approximately 80 % of land plants that have been investigated so far.¹⁸² Among mycorrhizas the arbuscular mycorrhiza, a form of endomycorrhiza, is dominant. While arbuscular mycorrhizas are formed solely by fungi of the division Glomeromycota,¹⁸³ ectomycorrhizas are mostly formed by basidiomycetous fungi.¹⁸² In an mycorrhizal association the fungus benefits from the associated plant since it provides the fungus with carbohydrates.¹⁸⁴ In turn, the plant benefits from the capability of the fungal mycelium to absorb water and mineral nutrients, such as phosphate¹⁸⁵ and nitrogen.¹⁸⁶ Consequently, mycorrhization is particularly advantageous for plants that grow on nutrient-poor soils. In general mycorrhized plants are more resistant to microbial pathogens¹⁸⁷ and to metal contaminations¹⁸⁸ in the soil than non-mycorrhized plants.

While it is well-known which nutrients are exchanged between fungi and plant roots, the signalling compounds that establish mycorrhiza formation, regulate nutrient exchange and influence plants and other interaction partners, such as soil bacteria and fungal endophytes are still not well-investigated. However, considerable progress has been made in the last decade, when the genomes from arbuscular and ectomycorrhizal fungi, such as *Laccaria bicolor*, *Paxillus involutus* and *Tuber melanosporum*, and their hosts became available.¹⁸⁹ By molecular biological manipulations it is now possible to generate transgenic plants and fungi and to develop sensitive and specific assays for the

detection of signalling compounds.

By this means it has been shown, that arbuscular mycorrhization is induced by the plant by release of the strigolactones, such as 5-deoxystrigol (**87**), that induces branching of arbuscular mycorrhizal fungi hyphae.¹⁹⁰ In turn the fungus generates lipochitoooligosaccharides, for instance **88**, that prepare the plant for fungal invasion.³⁰ In the case of ectomycorrhiza, fungi, such as *Tuber borchii* and *L. bicolor*, produce 2-(1*H*-indol-3-yl)acetic acid (IAA, **29**) and ethylene in order to control the morphology of the roots.¹⁹¹



In general, mycorrhization seems to have protective effects against below-ground herbivores. Although there are not many studies on plant-insect interactions in below-ground systems, investigations with several species of milkweeds, such as *Asclepias perennis* that were either uninoculated or inoculated with arbuscular mycorrhizal fungi, such as *Glomus intrradices*, showed that more inoculated plants survived in comparison to uninoculated ones.¹⁹² In accordance with these results, mycorrhized species of *A. perennis* also produced higher amounts of insecticidal cardenolides than the corresponding non-mycorrhized plants.¹⁹² For future studies it will be important to take all relevant interaction partners, such as insects and bacteria, into account in order to be able to gain a better understanding of the chemical ecology of mycorrhizal fungi and the corresponding plants.

Plant roots can also benefit from mycoparasitic fungi, such as *Trichoderma* species, that are associated with many plant roots and prevent plant-pathogenic fungi exerting negative effects on plant roots (see section 2.4.1).¹⁹³

2.3.3) Lichens

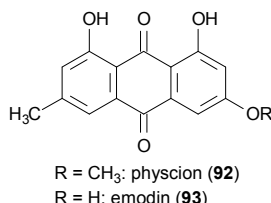
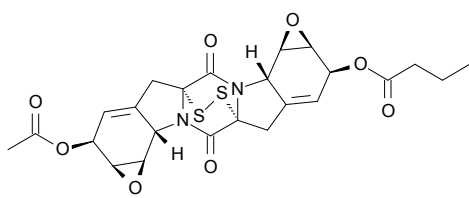
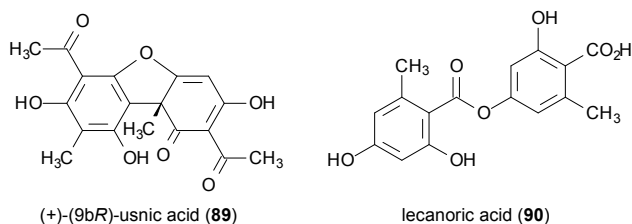
A lichen is an organism consisting of a fungus which is living together with an alga in a symbiotic relationship.²⁵ Although more than thousand secondary metabolites are known from lichens,²⁵ the ecological role of most of these compounds is still obscure, since only some lichen metabolites have been investigated in this regard.

For instance, the dibenzofurane derivative usnic acid (**89**) exhibits antifeedant activity besides antibiotic and antileukemic properties.¹⁹⁴ Usnic acid (**89**) is very widespread in lichen species, occurs both in the *R* and in the *S* form in lichens and

exhibits growth inhibitory effects against fungal plant pathogens and antifeedant activity and toxicity against insects, such as larvae of *Spodoptora littoralis*.¹⁹⁴

Vulpinic acid (**11**) is a pulvinic acid derivative that occurs in some lichens, for instance in *Letharia vulpina*.¹⁹⁵ It acts as strong toxin (see section 2.2.1.1). Vulpinic acid exhibits potent antifeedant activity against slugs and protects lichens from feeding on them.¹⁹⁶

Lichens usually contain so-called depsides, metabolites that consist of a phenolic acid that is esterified with another phenol. One of these depsides is lecanoric acid (**90**), which is widespread in lichens and exhibit antifungal activity.¹⁹⁷ By this means lichens are protected against many parasitic fungi.



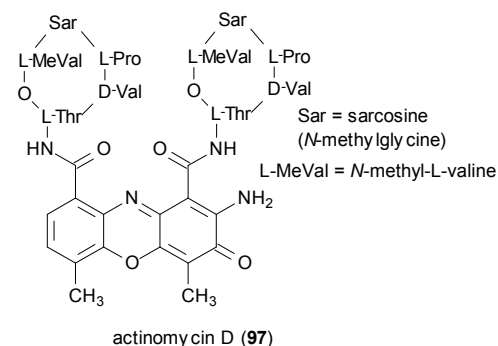
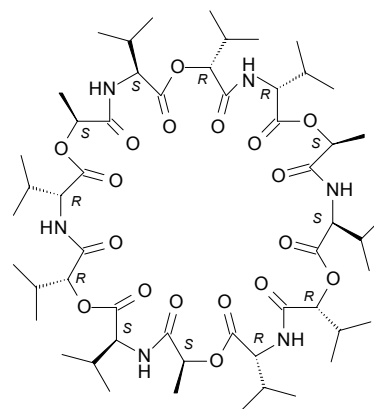
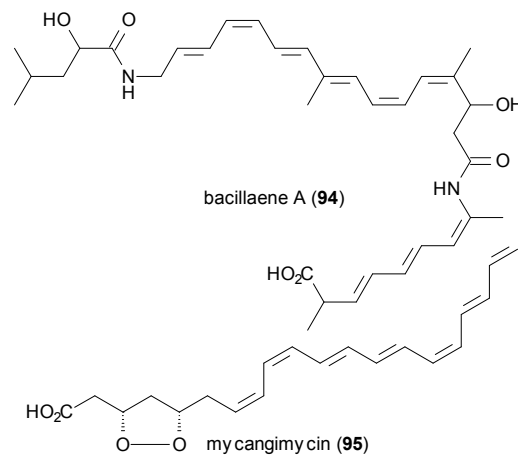
The lichen *Xanthoparmelia scabrosa* produces different scabrosin esters containing an unusual epidithiodioxopiperazine moiety, for instance ambewelamide A (**91**).¹⁹⁸ These compounds exhibit strong antiproliferative activity by targeting the mitochondrial ATP synthase in murine leukemia P388 tumour cells.¹⁹⁹ The antiproliferative activity might also affect pathogenic fungi and insects, thus protecting *X. scabrosa* from predators and competitors.

Many lichens, for instance *Candelaria* and *Xanthoria* species, contain anthraquinone pigments, such as physcion (**92**) and emodin (**93**). These compounds may serve as photoprotectants since they exhibit a strong UV absorption.²⁰⁰ Moreover, physcion inhibits plant growth²⁰¹ and both **92** and **93** show antibacterial and antifungal properties, for instance against the mould *Blumeria graminis*,²⁰² thus probably protecting lichens from nutrition competitors.

2.3.4) Symbiosis between Insects and Fungi

An important driving force for the establishment of a symbiotic relationship between insects and fungi might be the disability of most animals to digest cellulose. In contrast, many fungi contain cellulases that enable them to degrade this polysaccharide and use

it as nutrient.²⁰³ Especially different species of bark beetles, leaf-cutting ants and termites live in symbiosis with fungi. Due to the deleterious effects of some of these fungi, at least some of the interactions between insects, pathogenic fungi and their host plants have been studied in some detail.



For instance, the termite species *Macrotermes natalensis* grows antagonistic basidiomycete *Termitomyces* cultivar fungi.²⁰⁴ These fungi provide the termites enzymes, such as cellulases, which enable the termites to degrade plant material. In turn, the termites clean their fungus gardens, thus protecting them from infestation by mycoparasitic fungi, such as *Trichoderma* species.²⁰⁴ Moreover, the termites harbour a *Bacillus* species which produces

the antibiotic bacillaene A (**94**) that inhibits antagonistic fungi of *Terminomyces*.²⁰⁴

The southern pine beetle (*Dendroctonus frontalis*) live in symbiosis with the fungus *Entomocorticium* sp. A, which serves as nutrient for the beetle's larvae. In turn, the beetle inoculates galleries within the inner bark of the host pine tree and spreads the fungus within the tree.²⁰⁵ This symbiosis is endangered by the antagonistic fungus *Ophiomista minus* that is able to overgrow *Entomocorticium* sp. A. However, the symbiosis between *D. frontalis* and the *Entomocorticium* sp. A is supported by an actinomycete species, a bacterium, that produces the antibiotic mycangimycin (**95**) that selectively inhibits the growth of the antagonist *O. minus*.²⁰⁶

A similar kind of symbiosis is present between the elm bark beetle (*Scolytus multistriatus*) and the ascomycete *Ophiostoma novo-ulmi* leading to high mortality on European and North American trees of the genus *Ulmus* (see section 2.4.2).²⁰⁷

Also leaf-cutting ants, such as *Acromyrmex*, live in symbiosis with a fungus.²⁰⁸ These ants grow the fungus *Leucoagaricus gongylophorus* with harvested leaves inside their nests as major food source. This symbiotic relationship is challenged by pathogens, such as fungi belonging to the genera *Escovopsis*, *Fusarium* and *Trichoderma*.²⁰⁹ Therefore, the ants clean their fungus garden by mechanical means and secrete antimicrobial agents, for instance 3-hydroxydecanoic acid, from their metapleural glands.²¹⁰ Moreover, also in this case, a bacterial symbiont, a *Pseudonocardia* species, produces antibiotics, such as valinomycin (**96**) and actinomycin D (**97**), which inhibit the growth of insect-pathogenic fungi.²⁰⁹

Since bacteria living in symbiosis with fungi and insects turned out to be a rich source for new antibiotics, a systematic screening of these bacteria for antibiotics has already begun.^{211,212}

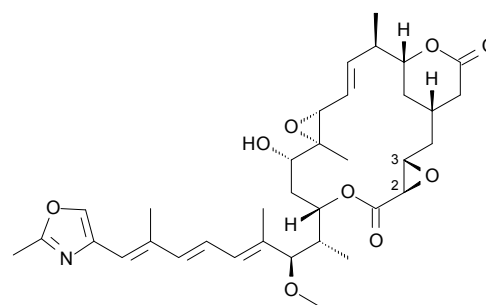
2.3.5) Symbiosis between Bacteria and Fungi

Bacteria are not only nutrient competitors for fungi. At least, some fungi benefit from bacterial secondary metabolites. However, many examples of this type of interaction are probably still unknown, since such interactions can easily be overlooked. To prove that secondary metabolites from bacteria support fungi it is either required to identify secondary metabolites which protect the host fungus in pure cultures of mycosymbiotic bacteria or to identify biosynthetic genes or proteins of secondary metabolites which are beneficial for the host fungus in the mycosymbiotic bacterium itself.

In the symbiosis between leaf-cutting ants and the fungus *L. gongylophorus* a *Pseudonocardia* species seems to play a decisive role. This bacterium produces the antibiotic valinomycin (**96**) to protect both the ants and the fungus from pathogenic fungi.²⁰⁸ Likewise, the termite *Macrotermes natalensis* hosts a *Bacillus* species which protects termite-symbiotic fungi from antagonistic fungi (see section 2.3.4).²⁰⁴

Several fungi of the genus *Rhizopus* are plant-pathogenic fungi causing rice seedling blight. Causative agent for the plant disease is the macrocyclic polyketide rhizoxin (**98**) that has been found in cultures of *Rhizopus* species. The phytotoxin inhibits mitosis in rice plants. However, it has been shown that the fungus itself does not produce rhizoxin but hosts an endosymbiotic bacterium of the genus *Burkholderia* that is the producer of WF-1360F, a direct precursor of rhizoxin (**98**), containing an *E* double bond

between C-2 and C-3 instead of the epoxide.^{213,214} The fungus itself epoxidises WF-1360F to the plant pathogen rhizoxin.²¹⁴ Therefore, the rhizoxin biosynthesis is an example for a biosynthetic synergism between a bacterium and a fungus.



rhizoxin (**98**)

2.4) Attack and Counter-Defence

Fungi are not only able to defend themselves against competitors and enemies or to live in symbiosis together with other organisms.

Many fungal species are pathogenic or parasitic and actively attack other fungi,²¹⁵ plants¹⁹³ or insects.²¹⁶ Pathogenic and parasitic fungi often use cell wall-degrading enzymes²¹⁷ and toxic secondary metabolites²¹⁸ to overcome the chemical defence of the hosts. Moreover, some species are capable to neutralise the host's chemical defence, thus exerting a counter-defence against the host (see section 2.4.2).²¹⁹

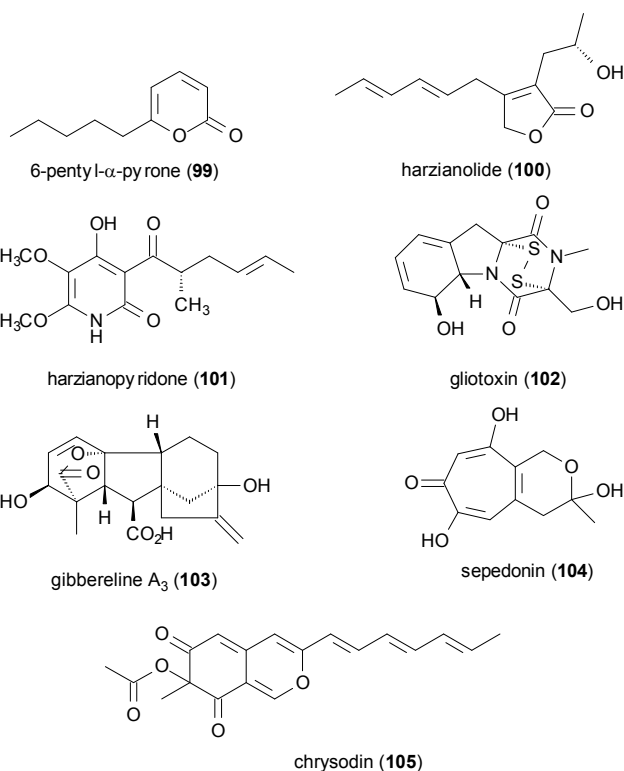
2.4.1) Mycoparasitic Fungi

Mycoparasitic fungi invade other fungal species and harm the host fungus.²¹⁵ While biotrophic mycoparasites do not kill the host but obtain nutrients from the host's tissues, necrotrophic mycoparasites kill the host and consume its tissues and nutrients.²¹⁵ Mycoparasitic fungi both occur on fruiting bodies of fungi²²⁰ and on fungal mycelia.²¹⁵ In general, mycoparasitic fungi, such as *Trichoderma* species, have developed several biocontrol mechanisms which act together synergistically.²²¹ For, instance, these mechanisms include the production of toxic compounds and antibiotics that harm the host's cells and of hydrolytic enzymes that degrade the hosts cell walls.²²² Moreover, Mycoparasitic fungi have the ability to resist potential toxic metabolites.²²³

Apart from a few mycoparasitic fungi, such as *Trichoderma* species, the chemical ecology of mycoparasitic fungi is not well investigated. *T. harzianum* and other *Trichoderma* species are soil-borne fungi that parasitize many other fungi.¹⁹³ Due to their antagonistic effects against many plant-pathogenic fungi and their use as biocontrol agents²²³ the constituents and properties of *Trichoderma* species have been studied in some detail.¹⁹³

To be able to be successful as soil organisms, *Trichoderma* strains tolerate fungistatic compounds present in the soil.²²² For instance, *Trichoderma* species are resistant to herbicides, fungicides, pesticides and phenolic compounds.²²⁴ Moreover, *Trichoderma* species are able to outcompete other fungi by production of highly efficient iron-chelating siderophores that lead to iron starvation of other less effective fungal species.²²⁵

To attack other fungi *Trichoderma* strains actively produce antibiotics and cell-wall-degrading enzymes.²²² Among the antibiotics is the volatile 6-pentyl- α -pyrone (**99**) which is highly effective against many plant pathogens, such as *Botrytis cinerea* and *Rhizoctonia solani*.²²⁶ Moreover, *Trichoderma* species produce the antibiotic harzianolide (**100**) and harzianopyridone (**101**).²²⁶ In *Trichoderma virens*, gliotoxin (**102**) plays an important role as antifungal agent.²²⁴ Among the cell-wall-degrading enzymes, chitinases, glucanases and proteases are present.²²⁷ In *Trichoderma* species antibiotics and cell-wall-degrading enzymes act synergistically together in the destruction of antagonistic fungi.²²²



Since *Trichoderma* strains are always associated with plant roots and stimulate both plant growth and plant defence, *Trichoderma* species might also be considered as plants symbiotic organisms (see section 2.3.2).²²⁸ To colonise plant roots *Trichoderma* strains have to be able to adhere and recognise plant roots in order to penetrate plant roots and to tolerate toxic metabolites produced by the plants.²²² This kind of interaction is modulated by plant flavonoids and fungal auxins and hydrophobins, small hydrophobic proteins, leading to morphogenetic changes, such as appressorium development.²²⁹ Since plants react to fungal invasion by production of phytoalexins, flavonoids, terpenoids, phenolic compounds and antimicrobial compounds *Trichoderma* species tolerate relatively large quantities of such compounds.²²⁸ Moreover, *Trichoderma* strains produce growth factors that stimulate the germination of plant seeds.²²² *Trichoderma* species might stimulate plant growth by production of secondary metabolites, such as 3-indolyl acetic acid (IAA, **29**) and gibberellin GA₃ (**103**).²³⁰ By secretion of organic acids, for instance fumaric and citric acid, phosphates and mineral cations

are solubilised.²²⁸ By these means the bioavailability of these compounds is increased.

Although there are many mycoparasitic species known that parasitise on fruiting bodies of fungi,²²⁰ in general, there is still not much known on their secondary metabolites and even less on their chemical ecology. One relatively well-investigated necrotrophic mycoparasite is *Sepedonium chrysospermum* that parasitizes fruiting bodies of Boletaceae, for instance *Boletus edulis*. It contains the polyketide sepedonin (**104**) that exhibits bioactivity against bacteria, yeasts and moulds^{231,232} and chrysodin (**105**) with antifungal activity.²³³ Moreover, peptaibols, antimicrobial peptides, which contain high proportions of γ -aminoisobutyric acid, such as the antibacterial and antifungal chrysospermins²³⁴ and the antibiotic chrysaibol,²³⁵ occur in *S. chrysospermum*. By these means *S. chrysospermum* might be able to secure its habitat from competing species. The virulence of this mycoparasite towards Boletaceae might be attributed to a so far not fully characterised haemolytic peptide.²³⁶

Some mycoparasitic fungi are able to parasitize lichens, despite the fact that lichens produce a variety of antibiotic secondary metabolites.^{237,219} For instance, a *Fusarium* species is able to degrade lecanoric acid, thus inactivating an important chemical defence compound of the lichens *Lasallia papulosa* and *Lasallia pennsylvanica*.²¹⁹ Consequently, in the presence of *Fusarium* species the lichenicolous fungus *Marchandiomyces corallinus* is able to grow on *L. papulosa* and *L. pennsylvanica*.²¹⁹ An analogous example is known from the lichen *Punctelia rudecta* which is parasitized by the lichenicolous fungus *Nectrina parmeliae* with the aid of a lecanoric acid degrading *Fusarium* species.²³⁸

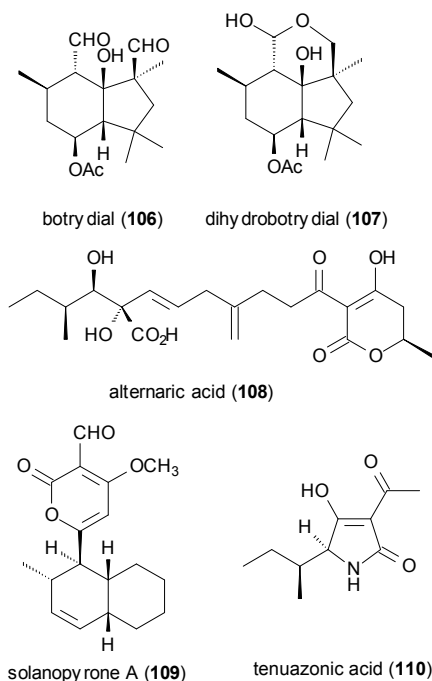
2.4.2) Plant Pathogenic Fungi

Plant pathogenic fungi are fungi that invade plants and cause plant diseases, such as wilting of leaves, necrotic lesions, cankers or shrivelled fruits.¹⁹³ Phytopathogenic fungi are able to destroy the crop of many food plants and have led to severe famine in the past. For instance, the oomycete *Phytophthora infestans* caused a disastrous potato blight in 1845 in Ireland, which ruined most of the Irish potato crop.¹⁹³ As a consequence of the highly negative impact of such fungi on food plants and on trees, many phytopathogenic fungi have long been subject of intensive investigations.

As well as mycoparasitic fungi, plant pathogenic fungi have developed means to invade host plants. Analogously to mycoparasitic fungi, biotrophic and necrotrophic plant pathogens are distinguished from each other.²³⁹ In general, germinating fungal spores are able to recognise surface glycoproteins and polysaccharides of host plants and invade host plants either through lesions or by degradation of the plant cell walls by secretion of cellulolytic enzymes.²¹⁵ After invasion into the host plant, necrotrophic fungi, such as *Alternaria*, *Botrytis*, *Fusarium*, *Helminthosporium*, *Ramularia*, *Sklerotinia* and *Verticillium* species, secrete degenerative enzymes and toxins into the plant tissues, leading to necrotic lesions and other symptoms of plant diseases.^{193,217} Biotrophic phytopathogenic fungi form haustoria, nutrient cells, which are required for the uptake of nutrients from the host plant by the pathogenic fungus.²³⁷

So far, a large number of plant pathogenic fungi and many different types of toxins have been described and summarised in reviews^{193,217,218,240} Consequently, this review presents only some

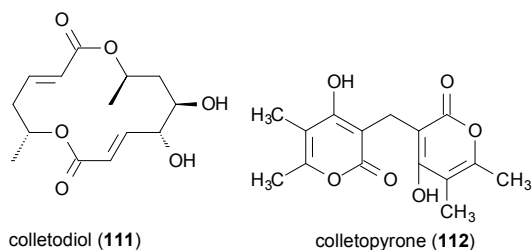
selected examples of plant pathogenic fungi.



The grey mould *Botrytis cinerea* is a phytopathogen that causes dark necrotic lesions on leaves and fruits of many plant species including several important crops, such as grapes strawberries and lettuce.^{193,241} The pathogenic fungus induces an oxidative burst during lesion formation in the plant by secretion of oxidative reactive species.^{242,243} Moreover, it produces phytotoxins, for instance botrydial (**106**) and dihydrobotrydial (**107**).²⁴⁴

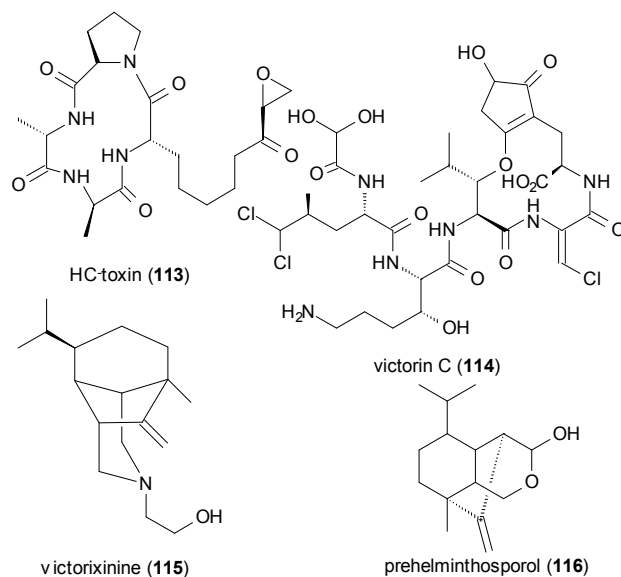
Alternaria species cause leaf-spot diseases on plants.¹⁹³ For instance, *Alternaria solani* is responsible for the early blight disease of potatoes and tomatoes.^{193,245} *A. solani* contains alternaric acid (**108**)²⁴⁶ that exhibits antifungal and phytotoxic activity.²⁴⁵ Moreover, in *A. solani* solanopyrone A (**109**) is present which causes necrotic lesions on potato leaves.²⁴⁷

The biotrophic phytopathogen *Pyricularia oryzae* causes rice blast disease.²⁴⁸ Both *P. oryzae* and *A. alternata* contain the phytotoxin tenuazonic acid (**110**)²⁴⁹ that hampers the development of rice seedlings.¹⁹³



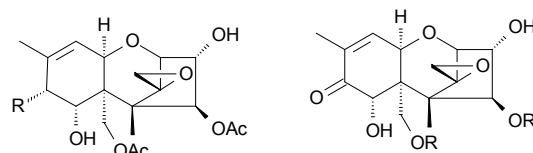
Plant pathogenic *Colletotrichum* species are responsible for necrotic spots on leaves and fruits, such as beans, grapes, pepper and tobacco.¹⁹³ For instance, *Colletotrichum capsici* is a pathogen of pepper and produces the phytotoxin colletodiol (**111**),²⁵⁰ while *C. nicotiana*, a pathogen of tobacco plants,

contains the phytotoxic colletopyrone (**112**).²⁵¹

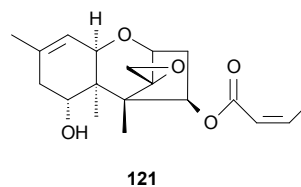


Helminthosporium species cause leaf spot diseases on grasses including wheat, maize, oats and rice.^{193,252} The phytotoxic cyclic peptide HC-toxin (**113**) occurs in *Helminthosporium carbonum*,²⁵² while victorin C (**114**)^{253,254} and victorixinine (**115**)²⁵⁵ have been found in *Cochlibolus victoriae*, the teleomorph (sexual stage) of *H. victoriae* (anamorph, asexual stage). Moreover, the phytotoxin prehelminthosporol (**116**)²⁵⁶ is present in *Bipolaris sorokiniana* (teleomorph: *H. sativum*). It inhibits the growth of coleoptiles of wheat.¹⁹³

Plant pathogenic fungi of the genus *Fusarium* are root-infecting fungi.¹⁹³ For instance, *Fusarium solani* causes root rots in beans and Solanaceae, while *F. graminearum* affects Graminaeae.¹⁹³ *Fusarium* species but also *Trichoderma*, *Trichothecium* and other fungi of the order Hypocreales²⁵⁶ contain phytotoxic trichothecenes,²⁵⁷ for instance T-2 toxin (**117**),²⁴⁰ and nivalenol (**119**).^{240,258} 4,15-Diacetylnivalenol (**120**) and diacetoxyscirpenol (**118**) isolated from *Fusarium equiseti* have been shown to be the ingredients that are responsible for the toxicity of this fungus to plant-feeding nematodes.²⁵⁹



R = OCOCH₂CH(CH₃)₂: T-2 toxin (**117**) R = H: nivalenol (**119**)
R = H: diacetoxyscirpenol (**118**) R = Ac: 4,15-diacetylnivalenol (**120**)



Moreover, the trichothecene **121** from *Spicellum roseum* exhibits antifungal activity.²⁶⁰ Consequently, trichothecenes might play a role in securing nutrients for the corresponding fungus.

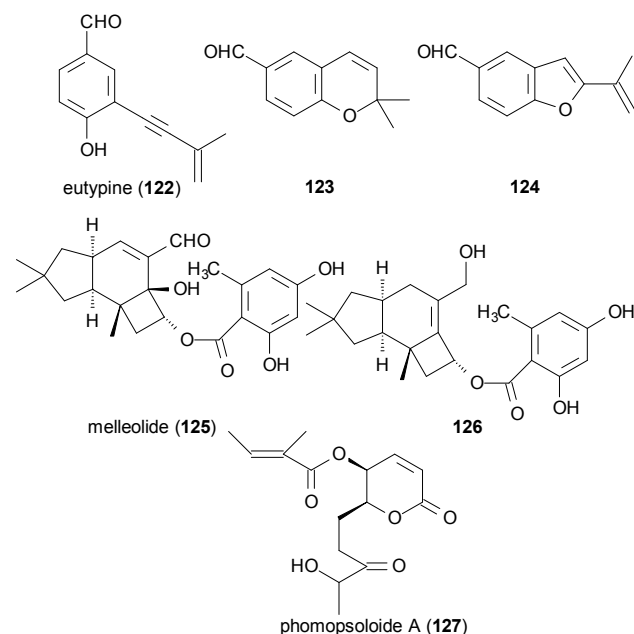
Consumption of trichothecenes by farm animals and humans leads to a wide range of toxic effects.²⁶¹ Induction of oxidative stress is an important mechanism of trichothecenes in exerting toxicity.²⁶¹ Among the different trichothecenes, T-2 toxin (**117**) is the most toxic to humans and farm animals.²⁶¹

Plant pathogenic fungi are also able to harm trees. For instance, eutypa dieback is a canker disease which affects trees, such as cherries, peaches and walnuts.^{193,262} The disease is caused by *Eutypa lata* which produces phytotoxin eutypine (**122**) and biosynthetically related metabolites, such as the chromene **123** and the benzofuran **124**.²⁶² Eutypine exerts its negative effect by uncoupling the oxidative phosphorylation in the host plant.²⁶³

Armillaria mellea is a basidiomycete which causes wood-rot in trees.¹⁹³ The fungus spreads in infected trees between the bark and the wood of the tree, thus blocking the tree's vascular system leading to the death of the tree.¹⁹³ Phytotoxins, such as melleolide (**125**)²⁶⁴ and armillyl orsellinate (**126**)²⁶⁵ help the fungus to exert its deleterious effects on trees.¹⁹³

The dutch elm disease has seriously affected elm populations in Europe and Northern America.¹⁹³ The disease is caused by the fungi *Ophiostoma ulmi* and *O. novo-ulmi* and the bark beetle *Scolytus multistratus*, which act symbiotically together in destroying *Ulmus* trees. The bark beetle bores galleries in the tree and transports the plant pathogenic fungi in these galleries.¹⁹³ The

fungi spread rapidly within the trees and produces the hydrophobic protein cerato-ulmin which causes the wilting and subsequent death of the tree.²⁰⁷ Interestingly, bark beetles are deterred from feeding on elms if the elms are infected by the fungus *Phomopsis oblonga* which produces beetle deterrents, such as phomopsolide A (**127**).²⁶⁶



Nowadays, phytotoxins from plant pathogenic fungi have become an interesting source for the development of new herbicides for control, since increase in regulatory requirements led to an increased demand for new herbicides.²⁶⁵

Plant-pathogenic fungi are not only successful in invading plants due to the production of toxins and other agents deleterious to

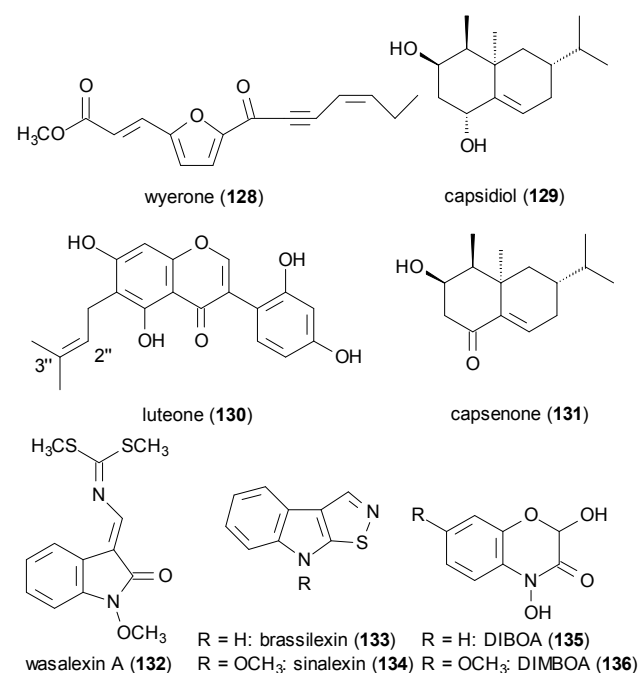
plants but also due to their ability to exert counter-defence to phytoalexins, metabolites that serve for plant defence purposes.

For instance, some plant-pathogenic fungi are able to detoxify such defence compounds.^{193,268}

To prevent infections with phytopathogenic fungi the bean *Vicia fabae* produces the phytotoxin wyerone (**128**),²⁶⁹ the pepper *Capsicum frutescens* capsidiol (**129**),²⁷⁰ and the lupin *Lupinus luteus* luteone (**130**).²⁷¹ However, some strains of *B. cinerea* are able to detoxify these compounds. For instance, wyerone is reduced to wyerol,²⁶⁹ capsidiol is oxidised to capsenone (**131**)²⁷² and luteone is converted to 2'',3''-dihydro-3''-hydroxyluteone and other less toxic metabolites.²⁷¹ However, the conversion of a plant metabolite by a fungus does not necessarily lead to compounds that are less toxic to fungi. For instance, the grape *Vitis vinifera* contains resveratrol that is oxidised by *B. cinerea* to ϵ -viniferin that turned out to be even more toxic to *B. cinerea* than resveratrol.²⁷³

In Brassicaceae (Cruciferae), for instance in rapeseed, cabbage and broccoli phytoalexins, such as wasalexin A (**132**), brassilexin (**133**) and sinalexin (**134**), are present.²⁶⁸ However, the phytopathogenic fungi *Leptosphaeria maculans* and *Sclerotinia sclerotiorum* are able to detoxify these defence compounds, thus enabling them to invade crucifers.²⁶⁸

Gramineae produce allelochemicals, such as the hydroxamic acids DIBOA (**135**) and DIMBOA (**136**).²⁷⁴ Nevertheless, the phytotoxic fungus *Gaeumannomyces graminis* var. *graminis* is able to infect Gramineae by degrading these defence compounds to inactive compounds.²⁷⁵



2.4.3 Entomopathogenic Fungi

To date more than 700 fungal species are known that are pathogenic to insects.²¹⁶ Most of the entomopathogenic fungi belong to the order Hypocreales.²¹⁶ Spores of entomopathogenic fungi attach to insects and germinate on them. Then, the developing hyphae penetrate the exoskeleton of the insects and

proliferate inside the insects, thus killing the host.²¹⁶ To do so, entomopathogenic fungi have developed tools for adhesion on the insect's surface and recognition of signalling compounds from the host.²⁷⁶ These tools include hydrolytic and detoxifying enzymes, such as esterases, chitinases, proteases and P450s, infectious structures, such as appressoria, and secondary metabolites that facilitate infection.²⁷⁶ On the other hand insects have evolved mechanisms to prevent infection, such as the generation of antifungal secondary metabolites and proteins or behavioural adaptations.²⁷⁶

Entomopathogenic fungi often can be easily identified as insect-pathogenic species, since they are attached to the host insect.

At least for more than thousand years the entomopathogenic fungus *Cordyceps sinensis* has been used in traditional Chinese medicine to treat various medical conditions, such as lung, kidney, liver and spine disorders.²⁷⁷ Moreover, entomopathogenic fungi, such as *Beauveria* and *Metarhizium* species have been developed as commercially available biopesticides.²⁷⁸ Nevertheless, the chemical ecology of many entomopathogenic fungi is still not well investigated.

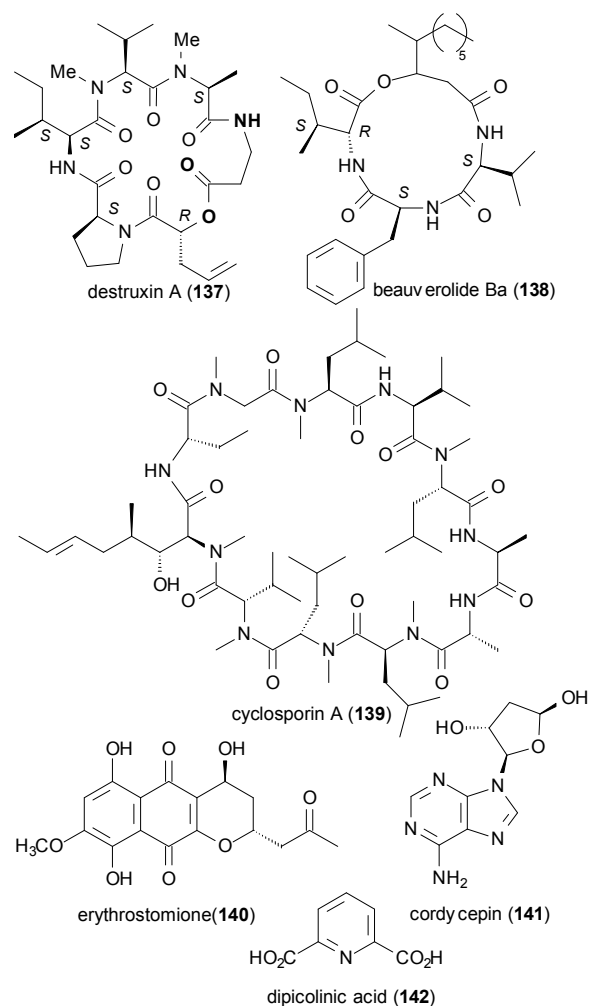
M. aniplosae is an entomopathogenic fungus with a broad host range. It produces a complex mixture of destruxins, such as destruxin A (**137**).^{279,280} The destruxins are cyclic depsipeptides, consisting of five amino acid residues and an α -hydroxycarboxylic acid moiety.²⁸⁰ In insects destruxins depolarise membranes by opening calcium channels, thus causing tetanic paralysis.²⁸¹

Moreover, *B. bassiana* contains cyclic depsipeptides, such as beauverolide Ba (**138**),²⁸² beauvericin,²⁸³ and bassianolide,²⁸⁴ while the entomopathogenic fungus *Cordyceps militaris* which, for instance, parasitizes silkworm chrysalis contains the closely related cordyceptide A.²⁸⁵ All depsipeptides exhibit insecticidal activity. Beauvericin is present in many hypocrealean fungi and exhibits potent cytotoxicity against human tumour cell lines.²⁸⁶

Cyclosporin A (**139**) is another insecticidal depsipeptide that was first isolated from *Tolypocladium niveum*, the anamorph of the entomopathogenic fungus *Cordyceps subsessilis*.²⁸⁷ However, cyclosporin A and its congeners did not become famous due to their insecticidal properties²⁸⁸ but due their use as powerful agents for the suppression of the immune response after organ transplantations in humans.²⁸⁹

Cordyceps unilateralis is a fungus that infects tropical ant species. After infection the fungus begins to affect the behaviour of the ant making it climbing up a plant stem and using its mandibles to fix itself to a leaf vein before killing the insect.²⁹⁰ Although the chemical basis of the behavioural manipulation is not well-investigated, it is at least known that *C. unilateralis* contains insecticidal naphthoquinones, such as erythrostrominone (**140**).²⁹¹

C. sinensis, parasitizing larvae of ghost moths,²⁹² and *Cordyceps militaris* parasitizing larvae of butterflies,²⁹³ are entomopathogenic fungi which produce the insecticidal cordycepin (**141**).^{292,293} Cordycepin has been identified as active ingredient of Traditional Chinese Medicines based on fruiting bodies of these fungi.²⁸⁸ The bioactivity of the nucleoside analogue cordycepin is attributed to its ability to inhibit DNA and RNA biosynthesis.²⁷⁷ Moreover, *Cordyceps militaris* produces the insecticidal pyridine derivative dipicolinic acid (**142**).²⁹⁴



Today, there is a considerable interest in secondary metabolites from entomopathogenic fungi due to the potent immunosuppressant and antitumour activities of several of their metabolites. For instance, more than 50000 papers have already been published about the cyclosporins. These activities are not present only by chance in entomopathogenic fungi, since antiproliferative and immunosuppressant properties are useful for entomopathogenic fungi to be able to invade insects. To develop more environmentally-friendly biopesticides it will be necessary to evaluate not only the potential of secondary metabolites for pest control but also for their ecological role.

3) Conclusions

Although this review covers the chemical ecology between fungi and many other organisms it was only possible to present selected examples. Moreover, many types of interactions but not all are presented in this review. For instance, dermatophytic fungi are not mentioned. Our current knowledge on the chemical ecology of fungi is still limited. While plant-fungi interactions and mycotoxins are subject of many investigations, there are still only a few reports on mycoparasitic fungi, on induced chemical defence in fungi and on fungal chemical communication. However, scientists become more and more aware that fungi are

important players in ecological communities. For instance, endophytic fungi and entomopathogenic fungi became subject of intensive research when their important role in the production of bioactive secondary metabolites, such as cyclosporin A (**139**) and paclitaxel (**85**), became obvious. Particularly in recent years the awareness grew that interactions are often not restricted to two organisms. Instead, multipartite communities with many interaction partners are often present. For instance, this is the case in the interaction between leaf-cutting ants, agonistic and antagonistic fungi and an agonistic bacterium. A better understanding of the chemical ecology of these communities is helpful for the discovery of new bioactive secondary metabolites which are desperately needed as potential lead structures for the development of new drugs. For instance, some active metabolites are generated only upon injury or in the presence of certain organisms. This has to be taken into account to be able to isolate such kinds of secondary metabolites. Consequently, studying fungal chemical ecology, particularly not well investigated areas, such as induced chemical defence and chemical communication in fungi, will not only deepen our knowledge but also provide new nature-inspired tools for pest control and drug development.

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