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Toxic terpenoids isolated from higher fungi

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A large number of toxic terpenoids have been isolated from cultures and fruit bodies of higher fungi. The chemistry, biological activity and possible natural functions of some of them are discussed in this paper. Especially interesting in this respect are natural defensive compounds that possess for example antibiotic and antifeedant activies and are likely to be toxic. The sesquiterpenoids of the pungent Lactarius species (e.g. L. necator, L. piperatus, L. rufus and L. vellereus) constitute an interesting example of this. In the fruit bodies of these species within seconds after an physical injury, an apparently inactive precursor is converted enzymatically into a range of pungent sesquiterpenes with an unsaturated dialdehyde functionality possessing potent antimicrobial and cytotoxic activities. The injury brings the precursor, which is present as an emulsion in the latex of specialised hyphae of the fruit bodies, in contact with the enzyme systems that are kept apart in the intact fruit body. Fruit bodies of non-pungent and edible Lactarius species (e.g. L. deliciosus and L. flavidulus) contain precursors with completely different chemical structures that also are converted as a response to injury, although to products with less striking biological activities and with uncertain function.

Key words: Terpenoids, toxicity, biological activity, higher fungi, Basidiomycotina

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Z kultur a plodnic vyšších hub bylo izolováno mnoho toxických terpenoidů. Je diskutována jejich chemie, biologická aktivita a u některých i možný jejich význam v přírodě. Zvláště zajímavé z tohoto pohledu jsou přírodní obranné sloučeniny antibioticky aktivní, které jsou pravděpodobně toxické. Sesquiterpenoidy palčivých druhů rodu Lactarius (např. L. necator, L. piperatus. L. rufus, L. vellereus) tvoří zajímavé příklady. V plodnicích těchto druhů jsou krátce po poškození inaktivní prekursory konvertovány enzymaticky do skupiny palčivých sesquiterpenů s nenasyceným dialdehydem, které působí silně antimikrobiálně a cytotoxicky. Při poškození plodnice jsou původně intaktní enzymatické systémy spuštěny a prekurzor emulgovaný v latexu mléčnic je aktivován. Plodnice nepalčivých a jedlých druhů rodu Lactarius (např. L. deliciosus, L. flavidulus) obsahují prekursory zcela jiného chemického složení, které jsou také konvertovány jako odpověď na poškození plodnice, avšak na produkty s méně nápadnými biologickými aktivitami a s nejistou funkcí.

INTRODUCTION

Although the terpenoids form the largest group of natural products (Connolly and Hill 1991) and are widespread in the kingdom of Fungi, it is conspicuous that only few of the classical mushroom poisons belong to the terpenoids. However, many of the terpenoids isolated from species belonging to the Basidiomycotina subdivision of Fungi possess potent toxic activities (Bresinsky and Besl 1985; Anke and Steglich 1988), and some of these are shown in Figure 1.

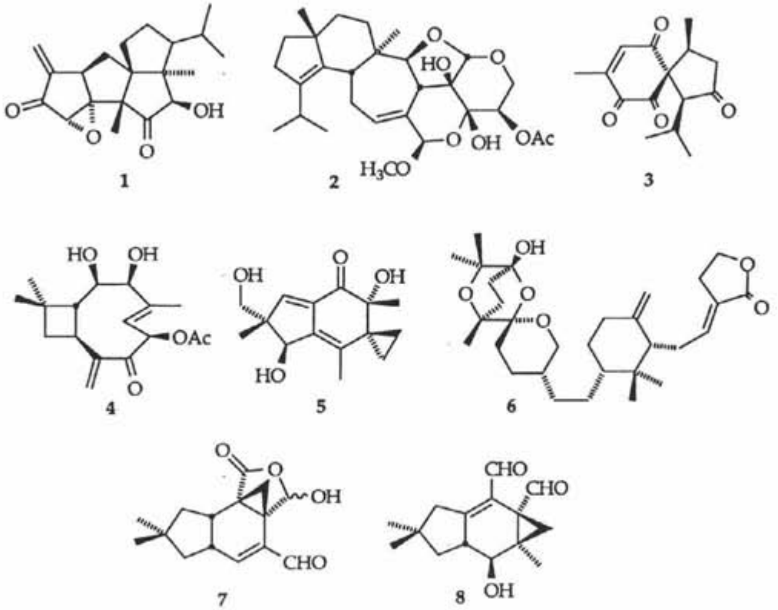

Figure 1

The crinipellins (e.g. crinipellin A [1]), are cytotoxic diterpenoids isolated from cultures of *Crinipellis stipitaria* (Anke et al. 1985), while the striatins (e.g. striatin A [2]) are produced by both cultures (Hecht et al. 1978) and fruit bodies (Rabe 1989) of *Cyathus striatus* as well as by other species. The LD_{50} value for striatin A (2) is 60-110 mg/kg (i.p. administration to tumour-bearing mice) (Douros and Anke 1994). The acorane hemimycin (3) was isolated from cultures of *Hemimycena cucullata* and *H. candida*, and possess potent cytotoxic activity (Bäuerle et al.1986). The fruit bodies of *Hypholoma fasciculare* have yielded a series of toxic triterpenoids, the fasciculols (Suzuki et al. 1983), and from cultures of several *Hypholoma* species the cytotoxic caryophyllane naematolon (4) was obtained (Backens et al. 1984). However, the toxicity of the latter toward mammals appear to be limited, as the LD_{50} value is well above 225 mg/kg (i.p. administration to tumour-bearing mice) (Douros and Anke 1994). Fruit bodies and cultures of *Omphalotus olearius* produce the toxic but also antineoplastic illudane illudin S (5) (McMorris and Anchel 1963). Several cytotoxic triterpenes, the saponaceolides, have been isolated from *Tricholoma* species, e.g. *T. saponaceum* (De Bernardi et al.

1988; 1991), and although their cytotoxic activity is remarkable (for saponaceolide B (6) ID_{50} on the LoVo cell line is 0.16 μg/ml, and LD_{50} on brine shrimps is 40 ng/ml) they possess no antimicrobial activity (De Bernardi et al. 1991). Two further examples of toxic sesquiterpenes are the mutagenic (Anke and Sterner 1991) marasmic acid (7) and merulidial (8), originally isolated from *Marasmius conigenus* (Kavanagh et al. 1949) and *Merulius tremellosus* (Giannetti et al. 1986), respectively. The LD_{50} value for marasmic acid (7) is 15-30 mg/kg (i.p. administration to tumour-bearing mice) (Dourns and Anke 1994).

THE SESQUITERPENES OF THE RUSSULACEAE SPECIES

The function of the terpenoids in the fungi, if any, is not clear. However, in the fruit bodies of the pungent species belonging to the genus *Lactarius* (family Russulaceae of the Basidomycotina subdivision) biologically active terpenoids are formed as a response to physical injury, in what appears to be a chemical defence system that protects the fruit bodies against parasites and infections (Camazine et al. 1983; Sterner et al. 1985a). In this, pungent metabolites with antifeedant and antimicrobial activity are formed when an inactive precursor is brought in contact with enzymatic systems by the injury, not unlike a binary weapon system. The precursor is present as an emulsion in the latex of the fruit bodies, this latex is characteristic for the *Lactarius* species and can be observed if a fruit body is cut or broken. The colour and taste of the latex, as well of the flesh, vary between different species, such characters areimportant taxonomic markers for mycologists and the chemistry related to these differences has been clarified for several species. Interestingly, there seems to a general pattern within the *Lactarius* genus, also in the non-pungent species, in that the metabolites responsible for the characteristic differences in taste and colour are formed enzymatically from fatty acid ester precursors as a response to injury to the fruit bodies. Depending upon the precursor originally present in the fruit bodies, the *Lactarius* species and the metabolites may be divided into three major groups:

1. The largest is made up by species belonging to the *Albati* and *Lactarius sections*, for example *L. vellereus, L. piperatus* and L. *scrobiculatus.* They generally have white latex containing large amounts of a biologically inactive fatty acid ester of a marasmane sesquiterpene which rapidly (in seconds) is converted enzymatically to bioactive marasmane, lactarane and seco-lactarane sesquiterpenes as a response to injury (vide infra).
2. In the species belonging to the Dapetes section of *Lactarius* (e.g. *L. deliciosus, L. deterrimus*, and *L. sanguifluus*) the latex is initially carrot-coloured or wine-coloured but slowly turns green. This has been shown to be due to the presence of stearic acid esters of guaiane sesquiterpenes in the intact fruit bodies which

are converted mainly by ester hydrolysis and oxidation to guaiane alcohols and aldehydes in the injured fruit bodies (vide infra).

3. The latex and flesh of the fruit bodies of species belonging to the *Plinthogali* section (e.g. *L fuliginosus* and *L. picinus*) is originally white and sweet, but due to the enzymatic hydrolysis of the stearic acid ester 9 to the free phenol 10 (a potent fungicid) and its enzymatic oxidation to a number of derivatives (e.g. the dimers 11 and 12) as a response to injury, the latex and flesh turn reddish and bitterly acrid (De Bernardi et al. 1992). Similar mixed phenolic/terpenoid metabolites, e.g. flavidulol A (13) and flavidulol C (14), possessing antimicrobial activity have been isolated from the fruit bodies of *L. flavidulus* (Takahashi et al. 1988; 1993; Fujimoto et al. 1993), a species not known in Europe.

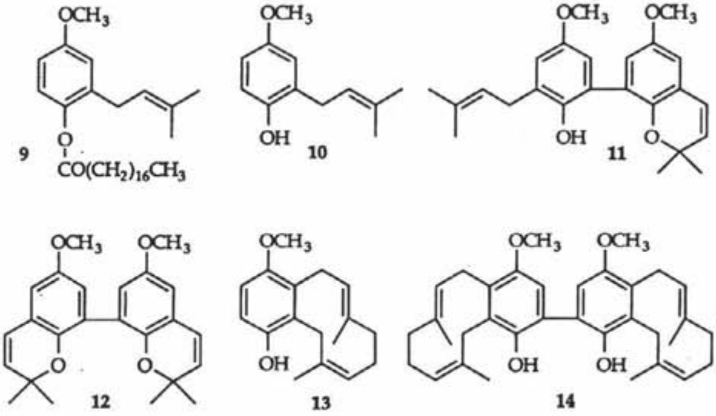

Figure 2

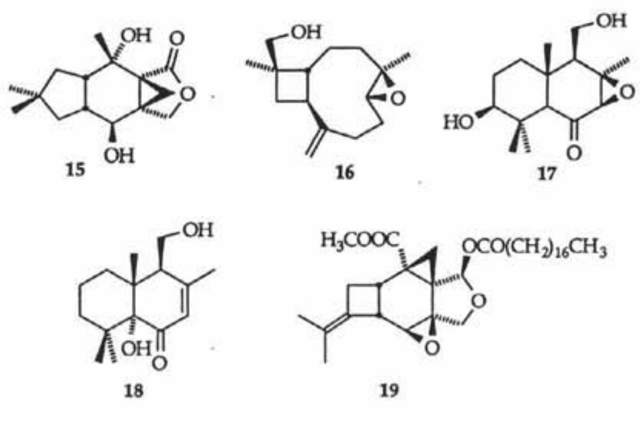

Figure 3

The isolactarane isolactarorufin (15) has in some investigations been isolated from extracts of *L. rufus* and *L. vellereus* (Daniewski et al. 1976a; 1988), species that mainly make marasmane and lactarane sesquiterpenes (vide infra). In addition, from fruit bodies of species belonging to other sections of *Lactarius*, sesquiterpenes with caryophyllane (compound 16 isolated from *L. camphoratus* [Daniewski et al. 1981]), drimane (e.g. uvidin A (17) and uvidin E (18) isolated from *L. uvidus* [De Bernardi el al. 1980; 1983]) and glutinopallal (e.g. stearoylglutinopallal (19) isolated from fruit bodies *of L. glutinopallens* [Fabre-Bonvin and Gluchoff-Fiasson 1988]) skeletons have also been identified.

A CHEMICAL DEFENCE SYSTEM IN THE PUNGENT LACTARIUS SPECIES

Isovelleral (20) and velleral (23) possess such striking biological activities that at least part of their function in for instance *L. vellereus* must be considered to be in a chemical defence system (Sterner et al. 1985a; Anke and Sterner 1991). In *L vellereus*, the two compounds are formed immediately after injury of a fruit body, and both compounds constitute 6 % of a hexane extract made 10 seconds after injury by grinding a fruit body in a meat grinder (Sterner et al. 1985a). The dialdehydes are subsequently reduced to isovellerol (21) and vellerol (24), and after several hours it was observed that small amounts of vellerol (24) had been further reduced to the corresponding diol (Sterner et al. 1985a). The reduced derivatives have lost the pungency and most of the biological activities of the unsaturated dialdehydes (Sterner et al. 1985b; 1987). No further conversion of isovellerol (21) was observed in this investigation, although the marasmane lactone 22, a possible oxidation product of isovellerol (21) (vide infra), has later been isolated from extracts of *L. vellereus* prepared in a different way (Daniewski et al. 1992a). In fruit bodies of *L. bertillonii*, only velleral (23) is formed from the precursor stearoylvelutinal (38b), velleral (23) is then reduced to vellerol (24) which subsequently is oxidised to vellerolactone (25) by the injured mushroom tissue (Hansson et al. 1994). Piperdial (26), piperalol (27) and blennin A (28) have been isolated from fruit bodies of for example *L. torminosus* (Seppä and Widen 1980; Sterner et al. 1985b), while the epimers epi-piperdial (29), epi-piperalol (30) and lactarorufin N (31) were isolated from the fruit bodies of *L. necator* (Daniewski et al. 1976b; Sterner 1989). Chrysorrhedial (32), chrysorrheal (also called scrobicalol) (33) and lactaroscrobiculide A (34) have been isolated from fruit bodies of *L. scrobiculatus* (Pang et al. 1992; De Bernardi et al. 1993) and *L. chrysorrheus* (De Bernardi et al. 1993). Lactardial (35) has been isolated from several species (Sterner et al. 1985b), for example *L. necator*, and its status as a natural product is somewhat questionable as it under certain circumstances may be formed as an artefact by chemical transformation of the velutinal esters (vide infra). However, it contains the unsaturated dialdehyde functionality, although in disguise, and it is pungent even if its antimicrobial activities and cytotoxicity are relatively weak compared with for instance isovelleral (20) and velleral (23) (Anke and Sterner 1991). The corresponding reduced form has been isolated in small amounts from *L. necator* in the form of lactarol (36) (reduction of the free aldehyde of lactardial (35) destabilises the dihydrohydroxyfuran functionality which spontaneously eliminates water to form the furan). Lactaronecatorin A (also called blennin C) (37) (Daniewski et al. 1975; structure revision Vidari et al. 1976) was obtained from the same species, and also from *L. blennius*.

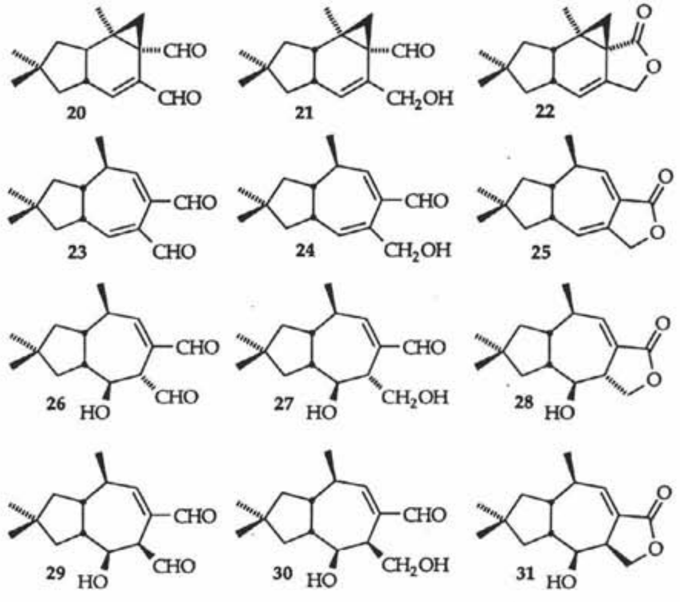

Figure 4

Besides the potent antimicrobial, cytotoxic and, in some cases, mutagenic activities of the unsaturated dialdehydes isolated from *Lactarius* fruit bodies (Anke and Sterner 1991), features that are shared with unsaturated dialdehydes isolated from other natural sources such as insects, molluscs and plants, an additional important quality is their intense pungent taste which actually make them excellent as human antifeedants. It has also been shown that mammals that normally feed on mushrooms will avoid edible specimens that have been treated with isovelleral (20) (Camazine et al. 1983). However, their pungency probably limits the hazard to consumers of wild mushrooms, as it would be difficult to consume significant amounts of the dialdehydes. 1 μg of for example isovelleral (20) (adsorbed on a filter paper disc) distinctly stimulates the taste-buds of the human tongue, and as 1 g of injured *L. vellereus* tissue may contain more than 1000 μg isovelleral (20) and velleral (23) only small amounts of the raw mushrooms can in practice be consumed by a normal individual. No toxicity tests with mammals have been performed, but the in vitro data suggest that the unsaturated dialdehydes would be highly toxic to mammals. The lactones, which appear to be the end-products in several species, also possess cytotoxic activity (De Bernardi et al. 1993).

The precursor of all the sesquiterpenes shown in Figure 4 is velutinal (38a) (Favre-Bonvin et al. 1982; Sterner et al. 1983), present as an emulsion (the latex) in specialised hyphae (Gluchoff-Fiasson and Kühner 1982) in the intact fruit bodies as various biologically apparently inactive (Sterner et al. 1985a) fatty acid esters (e.g. stearoylvelutinal (38b) in *L. vellereus* and *L. bertillonii* and 6-ketostearoylvelutinal (38c) in *L. necator* and *L. chrysorrheus*). The enzymatic conversions of stearoylvelutinal (38b) to form isovelleral (20), velleral (23), piperdial (26) and epi-piperdial (29) have been studied, and the biosynthetic pathways shown in Figure 5 have been proposed (Hansson et al. 1991; 1993). The formation of lactardial (35) during the enzymatic processes is probably similar to its formation from acid catalysed chemical transformation of the velutinal esters (vide infra), while the formation of chrysorrhedial (32) remains to be clarified.

In addition, quite a number of lactarane furans have been reported from the species yielding the compounds shown in Figure 4, although the majority of the furans are believed to be artefacts formed by chemical transformations of the labile velutinal esters (Sterner et al. 1985c). Traces of acid (present in for instance undistilled solvent or in chromatography gels) will rapidly transform any velutinal derivative to a number of dihydro-hydroxy-(acyloxy)-furans that easily eliminate water to form furans. As shown in Figure 6, some intermediates are carbocations that undergo additions, eliminations or rearrangements, and the product mixture obtained is rather complex. However, a few furans are actually formed as true natural products only in the enzymatic processes, e.g. the dihydroxyfuran 39 (see

Figure 6) (Sterner et al. 1988). Interestingly, some of the lactones and furans have been reported to possess antifeedant activity against storage pests (Daniewski et al. 1992b).

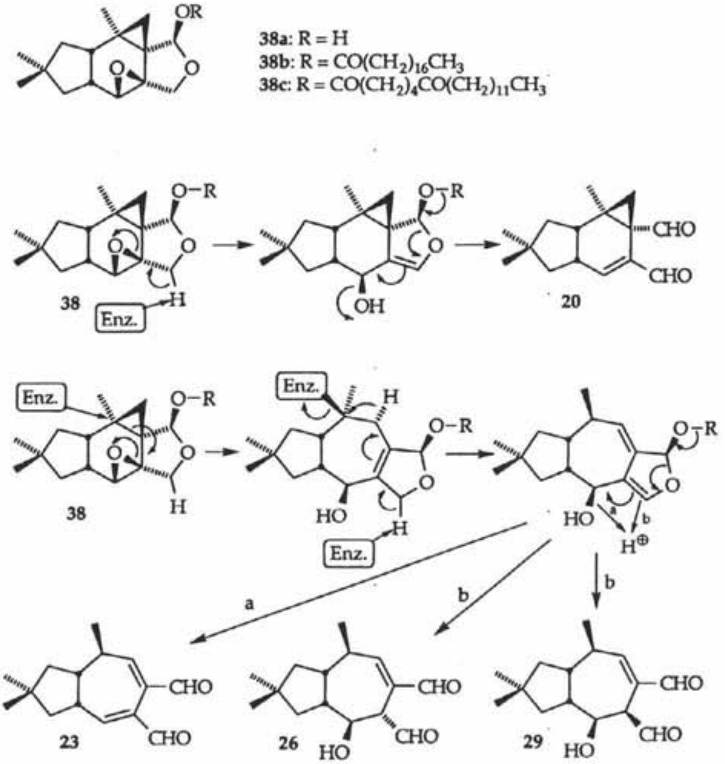

Figure 5

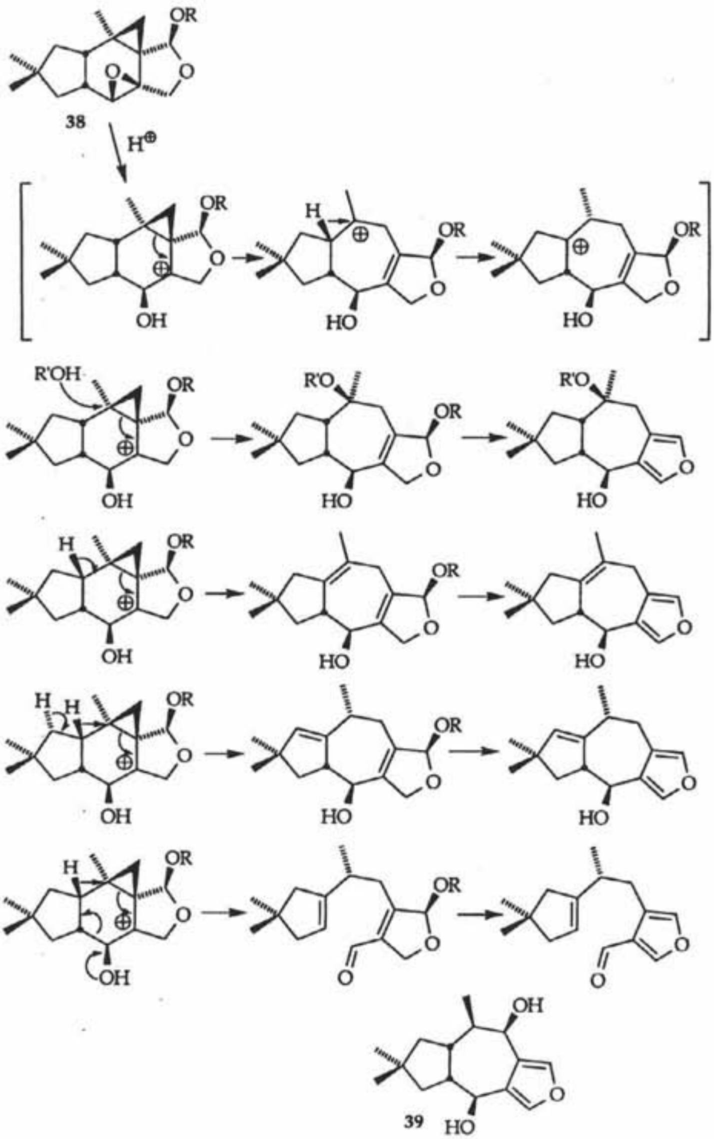

Figure 6

CONVERSIONS OF SESQUITERPENOIDS IN THE SAFFRON MILK CAPS (SECTION DAPETES)

Contrary to the pungent *Lactarius* fruit bodies which only are consumed in exceptional cases, the saffron milk caps are considered to be among the most desirable by consumers of wild mushrooms. They are characterised by strong and with time changing colours of the latex as well as by an agreeable peppery taste, but also by their lack of resistance to parasites compared to the pungent species. The colours of the latex are caused by the presence and formation of azulene and hydroazulene sesquiterpenoids with a guaiane skeleton, and the enzymatic conversions that take place as a response to injury resembles those of the pungent species in that the intact fruit bodies contain fatty acid (mainly stearic acid) esters of sesquiterpenes which are converted to sesquiterpenoic alcohols and aldehydes. The major differences are that the amounts of sesquitepenoids in the saffron milk caps are much smaller, that the enzymatic conversions are less rapid, and that the chemical functionalities present in the guaiane sesquiterpenes make them considerably less biologically active. In intact fruit bodies of *L. deliciosus* and *L. deterrimus*, only the orange ester 40 could be detected (together with minor amounts of the corresponding linolic acid ester) (Vokáč et al. 1970; Bergendorff and Sterner 1988). As a response to injury, 40 is slowly (minutes) converted by ester hydrolysis and oxidations to the dihydroazulenes alcohol 41 and delicial (42), as well as the azulenes deterrol (47) and lactaroviolin (48) (Bergendorff and Sterner 1988). The reduced azulene lactarazulene 49) was also detected in extracts of injured specimens, and it is believed that all these sesquiterpenes are formed enzymatically as they never could be observed as transformation products during work-up and isolation. Several of the compounds have been isolated in previous investigations of *L. deliciosus* and *L. deterrimus*, i.e. alcohol 41 (Vokáč et al. 1970), lactaroviolin (48) (Heilbronner and Schmid 1953), and lactarazulene (49) (Šorm et al. 1954). From Californian specimens of *L. deliciosus* lactarofulvene (50) was obtained (Bertelli and Crabtree 1968) while Indian specimens of *L. deterrimus* yielded the aldehyde 51 (Koul et al. 1985), although no traces of the latter two were seen in a recent investigation (Bergendorff and Sterner 1988), The green colour of the injured mushroom tissue emerges from a mixture of orange-yellow (40, 41 and 42) and violet-blue (47 and 48) compounds. The fruit bodies of *L, sanguifluus* originally contain a mixture of the orange 40 and the red 43, predominantly the stearic acid esters, which gives the latex its deep red colour (Sterner et al. 1989). Fruit bodies that had been injured (by grinding them in a meat grinder) for 30 minutes prior to extraction, yielded only sangol (44) (Sterner et al. 1989), although the aldehydes 45 and 51 previously have been isolated from *L. sanguifluus* (De Rosa and De Stefano 1981). The blue ester 46 has only been isolated from fruit bodies of *L. indigo*, which also yielded lactaroviolin (48) (Harmon et al. 1980).

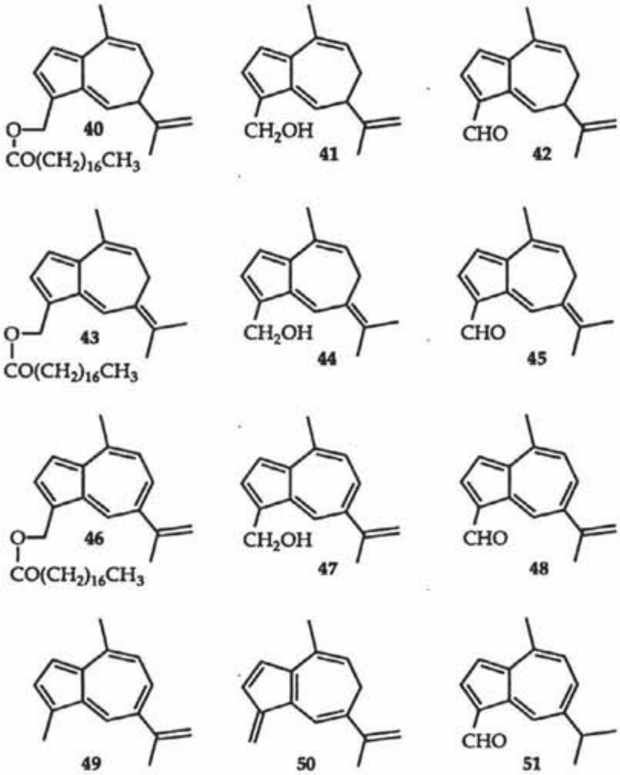

Figure 7

Although the bacteriostatic activity of lactaroviolin (48) was reported already in the 1940-ies (Willstaedt and Zetterberg 1946), the guaiane sesquiterpenoids formed in the saffron milk caps do not appear to affect humans otherwise than by colouring the urine. However, in vitro assays performed with compounds 40, 41 and 42 (which all are reasonable stable), showed that especially deterrol (41) possesses moderate cytotoxic activity (10 μg/ml inhibits the growth of ECA cells 50 %) and weak mutagenic activity towards Ames tester strains TA98 and TA100 (2.4 revertants/μg/plate) in the presence of rat liver extract (Anke et al. 1989).

CONCLUSIONS

The secondary metabolism of higher fungi has evolved during millions of years in order to increase the competitiveness of fungi, and produces a large number of biologically active and toxic compounds of which a substantial part is terpenoids.

Although the natural function of natural products in general is unknown, many have never the less been suggested to play roles for example as pheromones, as feedants, antifeedants or repellants, as regulators of the development of organisms as well as social behaviours, and in chemical defence systems. All such functions demand of a compound that it possesses biological activities, and the higher the activity is the more efficiently would it normally be able to perform its duties. The likelihood for such compounds to be toxic is therefore not negligible. In view of the fact that mushrooms have a low nutritional value and should be regarded more as a spice than as food in modern cuisine, one way to limit the risks to consumers is simply to avoid consuming excessive amounts of wild mushrooms.

REFERENCES

ANKE T., HEIM J., KNOCH F., MOCEK U., STEFFAN B. and STEGLICH W. (1985): Crinipelline, die ersten Naturstoffe mit einem Terquinan-Gerüst. – Angew. Chem. 97: 714-716.

ANKE T. and STEGLICH W. (1988): Neue Wirkstoffen aus Basidiomyceten. Forum Mikrobiologie 11: 21-25.

ANKE H., BERGENDORFF O. and STERNER O. (1989): Assays of the Biological Activities of Guaiane Sesquiterpenoids Isolated from the Fruit Bodies of Edible Lactarius Species. – Food Chem. Toxic. 27: 393-397.

ANKE H. and STERNER O. (1991): Comparison of the Antimicrobial and Cytotoxic Activities of Twenty Unsaturated Sesquiterpene Dialdehydes from Plants and Mushrooms. – Planta Med. 57: 344-346.

BACKENS S., STEFFAN B., STEGLICH W., ZECHLIN L. and ANKE T. (1984): Naematolin und Naematolon, zwei Caryophyllan-Derivate aus Kulturen von Hypholoma-Arten (Agaricales). – Liebigs Ann. Chem. 1332-1342.

BÄUERLE J., ANKE T., HILLEN-MASKE E. and STEGLICH W. (1986): Hemimycin, a New Antibiotic from Two Hemimycena Species (Basidiomycetes). Abstracts p. 4, 34th Ann. Congr. on Medicinal Plant Research in Hamburg.

BERGENDORFF O. and STERNER O. (1988): The Sesquiterpenes of Lactarius deliciosus and Lactarius deterrimus. – Phytochemistry 27: 97-100.

BERTELLI D. J. and CRABTREE J. H. (1968): Naturally Occurring Fulvene Hydrocarbons. – Tetrahedron 24: 2079-2089.

BRESINSKY A. and BESL H. (1985): Giftpilze, ein Handbuch für Apotheker, Ärzte und Biologen. Wissenschaftlische Verlagsgesellschaft, Stuttgart.

CAMAZINE S., RESCH J., EISNER T. and MEINWALD J. (1983): Mushroom Chemical Defence: Pungent Sesquiterpenoid Dialdehyde Antifeedant to Opossum. – J. Chem. Ecology 9: 1439-1447.

CONNOLLY J. D. and HILL R. A. (1991): Dictionary of Terpenoids, Vol. 1 – 3. Chapman and Hall, London.

DANIEWSKI W. M., KOCOR M. and KROL J. (1915): Two New Sesquiterpenoic Lactones from Lactarius necator. – Bull. Acad. Pol. Sci. 23: 637-641.

DANIEWSKI W., KOCOR M. and THOREN S. (1976a): Isolactarorufin, a Novel Tetracyclic Sesquiterpene Lactone from Lactarius rufus. – Heterocycles 5: 77-84.

DANIEWSKI W., KOCOR M. and KROL J. (1976b): Lactarorufin N and Revised Structures of Lactarorufins. Roczniki Chemii Ann. Soc. Chim. Polonorum 50: 2095-2100.

DANIEWSKI W., GRIECO P., HUFFMAN J., RYMKIEWICZ A. and WAWRZUN A. (1981): Isolation of 12-Hydroxycaryophyllene-4,5-oxide, a Sesquiterpene from Lactarius camphoratus. – Phytochemistry 20: 2733-2734.

DANIEWSKI W. M., KROSZCZYNSKI W., SKIBICKI P., DE BERNARDI M., FRONZA G., VIDARI G. and VITA-FINZI P. (1988): Normarasmane Sesquiterpenes from Lactarius vellereus. – Phytochemistry 27: 187-191 .

Daniewski W. M., Gumulka M., Ftaszynska K., Skibicki P., Krajewski J. and Gluzinski P. (1992a): Marasmane Lactones from Lactarius vellereus. – Phytochemistry 31: 913-915.

Daniewski W. M., Gumulka M., Gluzinski P., Krajewski J., Pankowska E., Ptaszynska K., Sitkowski J. and Bloszyk E. (1992b): 3-Ethoxy Lactarane Sesquiterpenes of Lactarius Origin Antifeedant Activity. – Pol. J. Chem. 66: 1249-1255.

De Bernardi M., Mellerio G., Vidari G., Vita-Finzi P. and Fronza G. (1980): Uvidins, New Drimane Sesquiterpenes from Lactarius uvidus Fries. – J. Chem. Soc. Perkin Trans. I 221-226.

De Bernardi M., Mellerio G., Vidari G., Vita-Finzi P. and Fronza G. (1983): Structure and Chemical Correlations of Uvidin C, D, and E, New Drimane Sesquiterpenes from Lactarius uvidus Fries. – J. Chem. Soc. Perkin Trans. I 2739-2743.

De Bernardi M., Garlaschelli L., Gatti G., Vidari G. and Vita-Finzi P. (1988): The Unprecedented Structure of Saponaceolide A, a Cytotoxic C-30 Terpenoid from Tricholoma saponaceum. – Tetrahedron 44: 235-240.

De Bernardi M., Garlaschelli L., Toma L., Vidari G. and Vita-Finzi P. (1991): The Structure of Saponaceolides B, C and D, New C-30 Terpenoids from Tricholoma saponaceum – Tetrahedron 47 : 7109-7116.

De Bernardi M., Vidari G., Vita-Finzi P. and Fronza G. (1992): The Chemistry of Lactarius fuliginosus and Lactarius picinus. – Tetrahedron 48: 7331-7344.

De Bernardi M., Garlaschelli L., Toma L., Vidari G. and Vita-Finzi P. (1993): The Chemical basis of Hot-tasting and Yellowing of the Mushrooms Lactarius chrysorrheus and L. scrobiculatus. – Tetrahedron 49: 1489-1504.

De Rosa S. and De Stefano S. (1987): Guaiane Sesquiterpene from Lactarius sanguifluus. – Phytochemistry 26: 2007-2009.

Douros J. and Anke T. (1994): Personal Communication.

Favre-Bonvin J., Gluchoff-Fiasson K. and Bernillon J. (1982): Structure du Stearylvelutinal, Sesquiternoide Naturel de Lactarius velutinus Bert. – Tetrahedron Lett. 24: 1907– 1908.

Favre-Bonvin J. and Gluchoff-Fiasson K. (1988): Structures of Two Glutinopallal Esters, New Natural Sesquiterpenoids from Lactarius glutinopallens. – Phytochemistry 27: 286-287.

Fujimoto H., Nakayama Y. and Yamazaki M. (1993): Identifcation of Immunosuppressive Components of a Mushroom, Lactarius flavidulus. – Chem. Pharm. Bull. 41 : 654-658.

Giannetti B. M., Steffan B,, Steglich W., Quack W. and Anke T. (1986): Antibiotics from Basidiomycetes. Part 23. Merulidial, an Isolactarane Derivative from Merulius tremellosus. – Tetrahedron 42: 3579-3586.

Gluchoff-Fiasson K. and Kühner R. (1982): Le Principe Responsible du Bleuissement au Reactif Sulfovanillique des Cystides ou Laticiferes de Divers Homobasidiomycetes; Interet Taxinomique. C.R. Acad. Sci. Ser. III 294: 1067-1071.

Hansson T. and Sterner O.(1991): Studies of the Conversions of Sesquiterpenes in Injured Fruit Bodies of Lactarius vellereus. A Biomimetic Transformation of Stearoylvelutinal to Isovelleral. – Tetrahedron Lett. 32: 2541-2544.

Hansson T., Pang Z. and Sterner O. (1993): The Conversion of [12-$^{2}H_{3}$]-Labelled Velutinal in Injured Fruit Bodies of Lactarius vellereus. Further Insight into the Biosynthesis of the Russulaceae Sesquiterpenes. – Acta Chem. Scand. 47: 403-405.

Hansson T., Sterner O. and Strid A. (1994): Chemotaxonomic Evidence for a Division of Lactarius vellereus and Lactarius bertillonii as Different Species. – Phytochemistry, submitted.

Harmon A. D., Weisgraber K. H. and Weiss U. (1980): Preformed Azulene Pigments of Lactarius indigo (Schw.) Fries (Russulaceae, Basidiomycetes). – Experentia 36: 54-56.

Hecht H.-J., Höfle G., Steglich W., Anke T. and Oberwinkler F. (1978): Striatin A, B and C: Novel Diterpenoid Antibiotics from Cyathus striatus; X-Ray Crystal Structure of Striatin A. – Chem Comm. 665-666.

Heilbronner E. and Schmid R. W. (1954): Azulenaldehyde und Azulenketone: Die Struktur des Lactaroviolins. – Helv. Chim. Acta 37: 2018-2039.

Kavanagh F., Hervey A. and Robbins W. J. (1949): Antibiotic Substances from Basidiomycetes. IV. Marasmius conigenus. – Proc. Natl. Acad. Sci. 35: 343-349.

Koul S. K., Taneja S. C., Ibraham S. P., Dhar K. L. and Atal C. K. (1985); A C-Forinylated Azulene from Lactarius deterrimus. – Phytochemistry 24: 181-182.

McMorris T. C. and Anchel M. (1963): The Structures of the Basidiomycete Metabolites Illudin S and Illudin M. – J. Am. Chem. Soc. 85: 831-832.

Pang Z., Bocchio F. and Sterner O. (1992): The Isolation of New Sesquiterpene Aldehydes from Injured Fruit Bodies of Lactarius scrobiculatus. – Tetrahedron Lett.33: 6863-6866.

RABE U. (1989): Fermentation von Cyathus striatus (Huds. ex Pers.) Willd. (Basidiomycetes) und Biosynthese der Striatine. Dissertation, University of Kaiserslautern (FRG).

SEPPÄ E.-L. and WIDEN K.-G. (1980): Sesquiterpenoids of Lactarius torminosus and L. trivialis and Correlation of the Sesquiterpenoid Composition of Lactarius Species with the Generic Subdivision. – Ann. Bot. Fennici 17: 56-60.

ŠORM F., BENEŠOVÁ V. and HEROUT V. (1954): – Coll. Czech. Chem. Comm. 19: 375.

STERNER O., BERGMAN R., KESLER E., NILSSON L., OLUWADIYA J. and WICKBERG B. (1983): Velutinal Esters of Lactarius vellereus and L. necator. The Preparation of Free Velutinal. – Tetrahedron Lett. 24: 1415-1418.

STERNER O., BERGMAN R., KIHLBERG J. and WICKBERG B. (1985a): The Sesquiterpenes of Lactarius vellereus and their Role in a Proposed Chemical Defence System. – J. Nat. Prod. 48: 279-288.

STERNER O., BERGMAN R., FRANZEN C. and WICKBERG B. (1985b): New Sesquiterpenes in a Proposed Russulaceae Chemical Defence System. – Tetrahedron Lett. 26: 3163-3166.

STERNER O., BERGMAN R., KIHLBERG J., OLUWADIYA J., WICKBERG B., VIDARI G., DE BEMARDI M., DE MARCHIF., FRONZA G. and VITA-FINZI P. (1985c): Basidiomycete Sesquiterpenes: The Silica Gel Induced Degradation of Velutinal Derivatives, – J. Org. Chem. 50: 950-953.

STERNER O., CARTER R. E. and NILSSON L. M. (1987): Structure-Activity Relationships for Unsaturated Dialdehydes 1. The Mutagenic Activity of 18 Compounds in the Salmonella/Microsome Assay. – Mutation Res. 188: 169-174.

STERNER O., WIK O. and CARTER R. E. (1988): The Structure of a Novel Fungal Sesquiterpene, Elucidated by Spectral and Computational Methods. – Acta Chem. Scand. B 42: 43-47.

STERNER O. (1989): The Co-formation of Sesquiterpene Aldehydes and Lactones in Injured Fruit Bodies of Lactarius necator and L. circellatus. The Isolation of epi-piperalol. – Acta Chem. Scand. 43: 694-697.

STERNER O., BERGENDORFF O. and BOCCHIO F. (1989): The Isolation of a Guaiane Sesquiterpene from Fruit Bodies of Lactarius sanguifluus. – Phytochemistry 28: 2501-2502.

SUZUKI K., FUJIMOTO H. and YAMAZAKI M. (1983): The Toxic Principles of Naematoloma fasciculare. – Chem. Pharm. Bull. 31:2176-2178.

TAKAHASHI A., KUSANO G., OHTA T. and NOZOE S. (1988): The Constituents of Lactarius flavidulus Imai. – Chem. Pharm. Bull. 36: 2366-2370.

TAKAHASHI A., KUSANO G., OHTA T. and NOZOE S. (1993): Revised Structures of Flavidulos Constituents of Lactarius flavidulus Imai, and the Structure of Flavidulol D. Chem. Pharm. Bull. 41: 2032-2033.

VIDARI G., DE BERNARDI M., VITA-FINZI P. and FRONZA G. (1976): Sesquiterpenes from Lactarius blennius. – Phytochemistry 15: 1953-1955.

VOKÁČ K., SAMEK Z., HEROUT V. and ŠORM F. (1970): The Structure of Two Native Orange Substances from Lactarius deliciosus – L. Coll. Czech. Chem. Comm 35: 1296-1301.

WILLSTAEDT H. and ZETTERBERG B. (1946): Lactaroviolin, ein gegen Tuberkelbacillen in vitro wirksames Antibioticum. – Svensk Kem. Tidskr. 58: 306-307.